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Economic Evaluations of Companion Cancer Biomarkers
for Targeted Therapies

MI KYUNG (KELLY) SEO

Thesis submitted in accordance with the requirements for the degree of
Doctor of Philosophy of the University of London

November 2020

Department of Health Services Research and Policy

Faculty of Public Health and Policy

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

Funded by Centre for Cancer Biomarkers (CCBIO), Bergen, Norway. CCBIO is established by Research
Council of Norway in collaboration with University of Bergen.

DECLARATION

I, Mikyung (Kelly) Seo, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed

A solid black rectangular box used to redact the signature of the author.

November 2020

ABSTRACT

Background

Companion biomarkers for targeted therapies have increased the expectation that biomarkers can improve health outcomes or potentially save health resources without compromising patient outcomes. However, few countries provide health economic assessment methods guidance (e.g. health technology assessment guide) specifically for co-dependent technologies such as companion diagnostics.

Aim

This thesis aims to explore good practices for evaluating companion biomarker tests as part of health economic assessments of their co-dependent targeted therapies in cancer.

Scope of the study

Cancer biomarkers for targeted therapies investigated in this thesis are restricted to companion biomarkers, classifying patients into responders and non-responders for a specific targeted therapeutic agent.

Methods

Four research activities were designed: two systematic literature reviews (SLR) and two health economic models. The first SLR (Chapter 2) was conducted to demonstrate the impact of companion biomarker tests on the cost-effectiveness of targeted therapies, focusing on metastatic colorectal cancer (mCRC). The second SLR (Chapter 3) considered all cancer areas. It investigated current and best practice for modelling and incorporating companion biomarker tests when assessing the cost-effectiveness of targeted cancer

therapies. The findings from these two SLRs were then applied to the cost-effectiveness modelling of a novel candidate companion biomarker test, Heat Shock Protein 27 (HSP27) expression (Chapter 4). The final work (Chapter 5) developed a practical guide to modelling companion biomarker tests as part of economic evaluations of corresponding targeted therapies; a global model was constructed and provided as a worked example coupled with step-by-step guide for readers to follow.

Results

The first SLR study showed that the use of companion biomarker tests saved some costs however, the saving was not high enough to change materially the cost-effectiveness of co-dependent therapeutic agents. The second SLR found that there was inconsistency in the methods for evaluating companion biomarker tests in the appraisal of co-dependent agents. The cost-effectiveness analysis of HSP27 expression showed conflicting results depending on the structure of the comparative analysis. Finally, the modelling guide coupled with a worked example of a global model demonstrated how to model characteristics of companion biomarker tests in economic evaluations of test-guided therapies.

Conclusion

This thesis highlights the need to reach a consensus on the methods of evaluating companion testing technologies as part of economic evaluations of their corresponding test-guided therapies. Built upon the consensus, a methods guide for co-dependent technologies needs to be developed and introduced, providing a coherent and unified guidance on good practices, reference case, evidentiary standards and data requirements for economic evaluations.

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Last but not least, my deepest thanks go to my husband, parents, parents-in-law, sisters and friends who have had confidence in me, encouraging and keeping me strong to persevere in every step of this journey. My special thanks go to all of my fellow PhD friends, Leesa, Kaiyi, Esther, Kaat, Jiyeon, Nour, Harriet who shared the same office; you all made my space full of joy and growth during this journey.

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ABBREVIATIONS

AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
Bmab	Bevacizumab
BSC	Best Supportive Care
CCBIO	Centre for Cancer Biomarkers
CDx	Companion Diagnostics
CEA	Cost-Effectiveness Analysis
CET	Cost-Effectiveness Threshold
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CIs	Confidence Intervals
Cmab	Cetuximab
CUA	Cost-Utility Analysis
DAP	Diagnostic Assessment Program
DSA	Deterministic Sensitivity Analysis
EE	Economic Evaluation
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EQ-5D	EuroQol-5D
EVPI	Expected Value of Perfect Information
FDA	Food and Drug Administration
HCS	Healthcare System

HE	Health Economic
HTA	Health Technology Assessment
HSP27	Heat Shock Protein 27
ICER	Incremental Cost-Effectiveness Ratio
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma
LS	Lynch syndrome
LSHTM	London School of Hygiene and Tropical Medicine
LYs	Life-Years
mCRC	Metastatic Colorectal Cancer
MM	Metastatic Melanoma
MT	Mutant
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NOK	Norwegian Krone
NoMA	Norwegian Medicines Agency
NSCLC	Non-Small-Cell Lung Cancer
OS	Overall Survival
PAP	Patient Assistance Program
PD	Progressive Disease
PFS	Progression-Free Survival
PGx	Pharmacogenetic/pharmacogenomic screening
PICOS	Population, Intervention, Comparator, Outcome, Study design
Pmab	Panitumumab

PSA	Probabilistic Sensitivity Analysis
PSM	Partitioned Survival Model
QALYs	Quality Adjusted Life Years
QALMs	Quality Adjusted Life Months
QHES instrument	Quality of Health Economic Studies instrument
RAS	Rat Sarcoma
RCTs	Randomized Clinical Trials
R&D	Research and Development
ROC	Receiver Operating Characteristic
ROI	Return of Investments
SLR	Systematic Literature Review
SOC	Standard of Care
SPC	Summary of Product Characteristics
UC	Usual Care
TC	Targeted Care
TK inhibitors	Tyrosine Kinase inhibitors
TT	Test-Treat
VEGF	Vascular Endothelial Growth Factor
VOI	Value of Information
WT	Wild-Type
WTP	Willingness-to-Pay

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1. INTRODUCTION

1.1. Aim, objectives, and scope of the study

1.1.1. Aim of the study

Overall, this thesis aims to explore good practices for conducting economic evaluations of companion biomarkers for targeted therapies in cancer. It intends to examine current and good practices for incorporating companion diagnostics when assessing the cost-effectiveness of their co-dependent therapies.

1.1.2. Objectives of the study

- **Objective 1.** To demonstrate the interaction between companion biomarker tests and targeted therapies in terms of the cost-effectiveness of biomarker-guided therapies. To show how the use of companion diagnostics affects the cost-effectiveness of their co-dependent targeted therapies. To discover whether or not the incorporation of companion diagnostics has led the co-dependent targeted therapies to be cost-effective. (*Chapter 2*).
- **Objective 2.** To explore current and best practices for modelling and incorporating companion biomarker tests when assessing the cost-effectiveness of the targeted therapies in cancer. To investigate current methods in modelling the characteristics of companion diagnostics based on the existing economic evaluations of biomarker-guided therapies in cancer. (*Chapter 3*).

- **Objective 3.** To apply study findings from previous literature reviews (Chapters 2,3) in a case study of modelling a novel companion biomarker test for targeted cancer therapy. To assess the cost-effectiveness of a novel candidate companion biomarker, Heat Shock Protein27 (HSP27) expression, for the use of bevacizumab in patients with metastatic melanoma; the treatment of patients with bevacizumab according to HSP27 expression status (intervention strategy arm) is compared with treating patients either with dacarbazine or bevacizumab without biomarker testing (comparator strategy arms). (*Chapter 4*).
- **Objective 4.** To provide a practical guide on how to conduct a cost-effectiveness analysis of cancer biomarkers for targeted therapies with worked examples of a core model. To demonstrate practically how to model and incorporate the characteristics of cancer biomarker tests as part of economic evaluations of the co-dependent targeted therapies. (*Chapter 5*).

1.1.3. Scope of the study

The cancer biomarkers for targeted therapies investigated in this thesis are restricted to companion biomarker tests (interchangeably, companion diagnostics) guiding the safe and effective use of therapeutics with its approved label restricting drug access (1). Companion biomarker tests inform on classifying/stratifying patients into responders and non-responders for the prescription of a specified therapeutic agent (in other words, biomarker-guided therapy). The technologies can be also the platforms used to deliver the companion diagnostic test. Different technologies can be used to provide the same diagnostic (2). Any other type of cancer biomarker tests such as complementary diagnostic tests that may inform on improving the benefit-risk ratio but does not restrict drug access

by labelling are beyond the scope of this study. The study type focused in this study is limited to model-based economic evaluations.

1.2. Background

The optimisation of treatment strategies has now become possible based on the information provided by biomarkers prior to treatment especially in oncology. With the increased knowledge in genetics and molecular biology, healthcare providers can be guided by biomarker tests when selecting treatments. This advance has raised expectations over personalised medicine or precision medicine, which aims to provide the right treatment to the right patient.

In this respect, biomarker-guided therapies may improve patient outcomes while helping to achieve efficient resource allocation in healthcare (4-7). In other words, companion biomarkers for targeted therapies have increased the expectation that biomarkers can improve health outcomes or potentially save health resources without compromising patient outcomes.

However, there is widespread scepticism about the research and development (R&D) of biomarkers and personalised medicine because the number of biomarkers successfully entering into routine clinical practice is very low compared to the number of biomarkers published (8-11). It might imply a significant time-lag between the development of rapidly evolving medical technologies and the implementation of them being actually used in clinical practice. Such lagged integration may potentially delay the improvement of patient outcomes or may even cause harms especially for patients unresponsive to the corresponding therapies. However, decision-making bodies for reimbursement of health technologies do not have unlimited budgets. It is inevitable for them to make a decision

reimbursing or funding intervention A over intervention B under the fixed budget in health care systems. “The opportunity cost of funding an intervention A would be the potential value or the difference (incremental benefits) of A compared to B and the difference in cost (incremental cost) of A compared to B” (12). Therefore, it is important to prioritize which intervention to be funded over the other ones based on health economic evidence generated by the comparative analysis of alternative courses of actions in terms of costs and benefits (i.e. economic evaluations). In economic evaluations, the opportunity cost of investing in a new intervention over standard care (or alternative interventions/health services) is measured by health benefits such as life years saved or QALYs gained (3). However, additional costs required by the introduction of new biomarker tests need to be justified by robust evidence of health economic benefits such as the value for money or cost-effectiveness (11, 13, 14). Therefore, the small number of biomarkers integrated into clinical practice could simply be a reflection on the quality of many of the biomarkers published. Then, the delayed integration or no introduction of new biomarker tests might be appropriate because the biomarkers published may not necessarily mean that they were worthwhile additions to clinical practices.

Therefore, it is of public interest to ensure the appropriate integration of new technologies into clinical use through adequate levels of reimbursement and coverage. However, it needs test developers or manufacturers to provide robust evidence on the health economic impact of biomarkers for targeted therapies. However, few countries provide health economic evaluation methods guide specifically to co-dependent technologies such as companion diagnostics (15, 16).

1.3. Companion cancer biomarkers for targeted therapies

The scope of this thesis is restricted to companion biomarkers that are essential for the safe and effective use of co-dependent health technologies (drugs or biological products) in cancer. A biomarker is defined as 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention' (5). A biomarker is not an assessment of how an individual feels, functions, or survives (17). Biomarkers have multiple uses in clinical practice, ranging from diagnostic, to prognostic and predictive purposes (5). Their clinical uses include screening the stage of disease, diagnosing the presence of disease, monitoring patients with regard to the intended effect or adverse effects of the treatment administered. Companion biomarkers for targeted therapies are used to predict response to specific treatments. Such predictive biomarkers are the key to integrate co-dependent health technologies such as biomarker-guided therapies into clinical use. Predictive biomarkers are used to identify individuals who are more likely to experience a favourable or unfavourable effect from a medical product or environmental agent than similar individuals without the biomarker (17). Companion diagnostics are predictive biomarker assays which are co-licensed with corresponding therapeutics and are linked to the use of a specific drug, so called 'test-drug' technology or co-dependent health technology. Recently, a new class of predictive biomarker assays emerged, called complementary diagnostics, along with the new regulatory approval of PD-1/PD-L1 immune checkpoint inhibitors for nivolumab or atezolizumab (18). However, in contrast with companion diagnostics, complementary diagnostics do not restrict patients from receiving co-dependent therapeutics because the therapeutic effect of complementary diagnostics is demonstrated in all patients regardless of biomarker status (19). According

to US FDA, companion diagnostic is defined as a medical device, often an in vitro device (IVD), which provides information that is essential for the use and effective use of a corresponding drug or biological product (1). HER2 assay for trastuzumab was the first companion diagnostic approved by US FDA in 1988 (20, 21). HER2 for trastuzumab is one of the examples of companion biomarker testing routinely used in clinical practice prior to the administration of targeted therapies to patients with breast cancer. In summary, companion diagnostics are required to prescribe the corresponding therapies only to responder subgroups of patients, whereas complementary diagnostics do not restrict the access to specific therapeutics but aid clinicians in benefit-risk decision-making. Therefore, this study focuses on the methods of economic evaluations of companion biomarker tests for targeted therapies in cancer.

1.4. Economic evaluations of biomarker-guided therapies

Economic evaluation is defined as a 'comparative analysis of alternative courses of action in terms of both their costs and their consequences' (3). Economic evaluations are conducted in order to provide health economic evidence to payers by comparing the health benefits and costs of new health technologies against those of existing technologies. They aim to assess the value for money of different strategies and to assist payers to make an informed decision on the resource allocation of scarce health services. In many countries, including the United Kingdom, economic evaluation is an integral part of health technology assessment (HTA) for new health technologies to be reimbursed and covered by health service providers (22, 23). In the UK (England), the National Institute for Health

and Care Excellence (NICE) provides a methods guide on technologies (with the general focus on medicines) (24), while providing a separate method guide on diagnostics and medical devices (25). In addition, for biomarker-guided therapies with rare incidence or low prevalence of biomarker status in the population, the NICE guide on highly specialised technologies for very rare conditions is applied (26).

Economic evaluation is also increasingly used to assess the value for money of diagnostics including cancer biomarker tests, although cancer biomarker tests are often assessed as a small component of economic evaluations of the corresponding drugs. Despite most countries providing clear guidance on the methods of economic evaluations for drugs (e.g. guide to the methods of technological appraisal (22, 23, 27)), only a few HTA methods guidelines exist for medical devices or diagnostics such as biomarker testing kits (28, 29) .

Furthermore, to our best knowledge, we found that very few countries provide a guide to the methods of health economic evaluation for co-dependent health technologies such as cancer biomarkers for targeted therapies such as, for example, Australia (15). Or, Scottish Medicine Consortium (SMC) includes a list of items to be completed if the applicant's health technology is companion diagnostics (16). However, for example, in England, NICE does not provide a specific guide to the methods of appraising the health economic evaluation of cancer biomarkers for targeted therapies (i.e. personalized medicine or precision medicine) but evaluates them according to the guide to the methods of technology appraisal, a document primarily (although not exclusively) developed with respect to the appraisal of pharmaceutical drugs (30, 31). This reflects the current reality that reimbursement bodies in many countries do not keep pace with the rapidly evolving health technologies such as 'omics'-based therapies with the integration of cancer biomarkers.

Reimbursement bodies make decisions based on robust evidence of clinical evidence and cost-effectiveness whether such introduction of new technologies provide more cost-effective health benefits to patients in comparison with existing technologies. In other words, the lack of evidentiary standards for cancer biomarkers influences payers' willingness to pay and cover the cost of new technologies (32, 33). Despite the increasing number of new biomarkers discovered, no agreement exists whether existing economic evaluation methods are sufficient to evaluate the health economic impact of biomarker tests (34, 35). Furthermore, it is not known whether different methodological approaches might produce conflicting results with regard to the cost-effectiveness of biomarkers or biomarker-guided therapies.

It is thus important to review and to suggest best practice for economic evaluation in assessing the value for money of cancer biomarkers for targeted therapies in the light of both methodological approaches and data requirements in constructing the health economic model.

1.5. Structure of the thesis

This thesis has been written as a series of individual research articles that can be read as stand-alone pieces of work but are integrated into a single document. The individual research articles are aligned with respective research objectives of this PhD thesis.

The thesis consists of six chapters that describe the studies that have been conducted to address the aim and objectives of this PhD research. Four research activities were designed to address the four specific objectives (Section 1.1.2) and presented in four respective research articles. Two systematic reviews and two cost-effectiveness model-based

analyses were performed and presented. Each separate objective has been answered by the following chapters, alongside original manuscripts published or prepared for publication.

First of all, Chapter 1 provides the overview of this thesis including aim and objectives, study focus/scope, study background and structure of the thesis. This chapter serves as an introduction to this thesis, guiding readers how individual articles are connected to each other and how they have contributed to the overall aim of the thesis. Besides, my contributions to the thesis, research funding and ethics approval have been declared in this chapter.

The first research article (Chapter 2) is a systematic literature review (SLR) titled “***Do Cancer Biomarkers Make Targeted Therapies Cost-Effective? Systematic Review in Metastatic Colorectal Cancer,***” published in PLOS One (36). This first SLR aimed to critically appraise economic evaluations of biomarker-guided therapies and to demonstrate the impact of biomarker tests on the cost-effectiveness of their corresponding targeted therapies, namely co-dependent health technologies, using the case of metastatic colorectal cancer (mCRC). All economic evaluations assessing companion diagnostics for targeted therapies in mCRC were searched and reviewed by two independent reviewers. Study selection was performed following the pre-defined criteria formulated by the PICOS framework (population, intervention, comparator, outcome, study type). This first SLR demonstrated whether the incorporation of companion biomarker tests has led the co-dependent targeted therapies to be cost-effective. It then informed me to the research question of the interaction between companion biomarkers and targeted drugs in terms of cost-effectiveness of biomarker-guided therapies. Furthermore, the quality of health economic studies (QHES) assessment performed as part of this first SLR study helped me

identify and develop key areas of methods to be focused on and investigated in the next SLR study.

The second research article (Chapter 3) is another SLR study titled ***“How Are We Assessing the Value for Money for Cancer Biomarkers in Economic Evaluations?”***, which is ready to submit for publication. This SLR aimed to investigate current and good practices for modeling and incorporating companion biomarker tests when assessing the cost-effectiveness of targeted cancer therapies. Extended from the first SLR study in one specific cancer case, this second SLR examined economic evaluations of companion biomarker tests in all cancer areas where companion diagnostics are routinely used prior to provision of the corresponding therapeutic agents. This review of companion biomarker tests was restricted to the companion diagnostics approved by the US Food and Drug Administration (37). Studies were selected according to pre-defined criteria of eligibility based on the PICOS framework. Studies that failed to report important information related to the companion biomarker test (e.g. biomarker characteristics or biomarker testing related data inputs) were excluded. Data extraction and analysis was performed based on the pre-defined key areas of methods, which were informed by my research in Chapter 2 and the CHEERS checklist (38). It critically reviewed how existing evaluations had considered the characteristics of companion biomarker tests in their cost-effectiveness assessments of co-dependent therapeutics.

I then applied the findings from these two reviews to the modelling of a novel candidate companion biomarker test, Heat Shock Protein 27 (HSP27) expression and evaluated the cost-effectiveness of HSP27 testing prior to the administration of bevacizumab. This research article (Chapter 4) is titled ***“HSP27 Expression as a Novel Predictive Biomarker for Bevacizumab: Is It Cost-Effective?”***, published in *Pharmacoeconomics – Open* (39). The

construction of this cost-effectiveness model was specifically informed by the previous SLR studies regarding the methods to incorporate the characteristics of companion biomarker tests in economic evaluations of the corresponding targeted therapies. HSP27 expression was chosen as a case study of modelling a companion biomarker test for a targeted therapy for three reasons. First, HSP27 expression was a novel candidate companion biomarker test discovered by my PhD research funder and it was of my funder's interest to be informed of the health economic value of this potential companion test for bevacizumab. Thus, the analysis was done from the perspective of Norwegian health system. Second, I had access to clinical data in relation to HSP27 expression and bevacizumab beyond the trial period reported in the published paper. Third, this biomarker allowed me to closely collaborate with oncologists/clinicians in assessing the cost-effectiveness of HSP27 expression.

Building upon the review findings and modelling practice acquired from previous research activities (Chapters 2-4), Chapter 5 provides a practical guide to modelling companion biomarker tests when assessing the cost-effectiveness of biomarker-guided co-dependent health technologies. This final research article (Chapter 5) is titled "***A Practical Guide to Conducting a Cost-Effectiveness Analysis of Companion Biomarkers for Targeted Therapies: Tutorial***", which is prepared for publication. This guide demonstrated in a practical manner how to construct the structure of alternative strategy arms including all relevant scenarios (e.g. test-treat strategy, treat-all with SOC without testing, treat-all with biomarker-guided therapy without testing). A core model was constructed and provided in R codes as a worked example for readers to follow. Readers (co-dependent technology developers, health economists, or modelers) can use this core model for local adaptations with appropriate adjustments according to their country-specific data requirements and HTA methods (e.g. reference case). This core model can guide the modelling data

requirements specifically relevant to companion biomarker tests as part of evaluating the value for money of biomarker-guided therapies. The R software was chosen to build this global model because it is open source (available free of charge), easily reproducible, and flexible compared to the other frequently used ones such as Excel®. The findings from all studies performed at the earlier stages of research activities in Chapters 2 to 4 assisted and informed the development of this core model.

My final chapter, Chapter 6 provides an overview of the main findings and discusses the limitations of this thesis, as well as the implications for further research, along with policy implications and evaluation recommendations in the assessment of companion cancer biomarkers in an economic evaluation of targeted therapies.

1.6. Contribution of the candidate to the thesis

I undertook two systematic reviews (Chapter 2-3) and took the lead in the planning of the study design, data extraction, data analysis and synthesis. I performed electronic literature searches and hand searches to identify relevant published publications. I screened all identified literature and reviewed full-text papers.

With regard to economic models (Chapter 4-5) included in this thesis, I designed and constructed both models and performed all cost-effectiveness analyses including survival analysis, value of information, and uncertainty analysis.

Overall, I was the primary investigator of all studies included in this thesis and wrote all manuscripts as the first author while my supervisors, John Cairns and Alec Miners, provided guidance and reviewed the manuscripts for publication.

More detailed descriptions of my contribution to each paper are provided in the title page of respective papers in the subsequent chapters.

1.7. Funding and ethics approval

This PhD was funded by the Centre for Cancer Biomarkers (CCBIO), University of Bergen, Norway and included tuition fees and an annual stipend over a period of 4 years.

Ethics approval was given by the London School of Hygiene and Tropical Medicine (LSHTM) ethics committee (LSHTM Ethics Ref: 11886). As part of my LSHTM ethical approval applications, the ethical approval letters confirmed for the clinical trial of the effect of bevacizumab monotherapy in the treatment of metastatic melanoma and predictive value of markers were submitted as the evidence of local ethics approval. Furthermore, the completed Data Management Plan for Research Students was submitted to LSHTM as part of my PhD upgrading assessment.

2. DO CANCER BIOMARKERS MAKE TARGETED THERAPIES COST-EFFECTIVE? A SYSTEMATIC REVIEW IN METASTATIC COLORECTAL CANCER

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	299429	Title	
First Name(s)	Mi Kyung (Kelly)		
Surname/Family Name	Seo		
Thesis Title	Economic evaluations of cancer biomarkers for targeted therapies		
Primary Supervisor	John Cairns		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	PLOS ONE		
When was the work published?	September 2018		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Yes	Was the work subject to academic peer review?	Yes

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Stage of publication	Choose an item.

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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	
--	--

SECTION E

Student Signature	
Date	

Supervisor Signature	
Date	29 November 2019

2.1. Research paper I

Title: Do Cancer Biomarkers Make Targeted Therapies Cost-effective? A Systematic Review in Metastatic Colorectal Cancer

Authors: Mikyung Kelly Seo^{1,2}, John Cairns^{1,2}

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Contribution of the candidate to this paper: I conceptualised this study together with John Cairns. I designed the literature search and review protocol based on the PICOS framework. I developed the search strategy per database where relevant studies were searched. I performed the literature search and identified studies fit with the purpose of this research. I performed the first and second screenings of title/abstract and full-text literature review. I developed and processed the data extraction for all studies identified relevant for the objective of this literature review study. I performed the data synthesis and analysis. I wrote and produced the first original manuscript and revised as needed.

ABSTRACT

Background

Recent advances in targeted therapies have raised expectations that the clinical application of biomarkers would improve patient's health outcomes and potentially save costs. However, the cost-effectiveness of biomarkers remains unclear irrespective of the cost-effectiveness of corresponding therapies. It is thus important to determine whether biomarkers for targeted therapies provide good value for money. This study systematically reviews economic evaluations of biomarkers for targeted therapies in metastatic colorectal cancer (mCRC) and assesses the cost-effectiveness of predictive biomarkers in mCRC.

Methods

A literature search was performed using Medline, Embase, EconLit, NHSEED. Papers published from 2000 until June 2018 were searched. All economic evaluations assessing biomarker-guided therapies with companion diagnostics in mCRC were searched. To make studies more comparable, cost-effectiveness results were synthesized as per biomarker tests and corresponding therapies. Methodological quality was assessed using the Quality of Health Economic Studies (QHES) instrument.

Results

Forty-six studies were included in this review. Of these, 17 studies evaluated the intrinsic value of cancer biomarkers, whereas the remaining studies focused on assessing the cost-

effectiveness of corresponding drugs. Most studies indicated favourable cost-effectiveness of biomarkers for targeted therapies in mCRC. Some studies reported that biomarkers were cost-effective, while their corresponding therapies were not cost-effective. A considerable number of economic evaluations were conducted in pre-defined genetic populations and thus, often failed to fully capture the biomarker's clinical and economic values. The average QHES score was 73.6.

Conclusion

Cancer biomarkers for targeted therapies in mCRC were mostly found to be cost-effective; otherwise, they at least improved the cost-effectiveness of targeted therapies by saving some costs. However, this did not necessarily make their corresponding therapies cost-effective. While companion biomarkers reduced therapy costs, the savings were not sufficient to make the corresponding agents cost-effective. Evaluation of biomarkers was often restricted to the cost of tests and did not consider their clinical values or biomarker prevalence.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the third leading cause of cancer deaths worldwide (40). In Europe, it is the most common cause of cancer death after lung cancer. In 2012, 241,600 men and 205,200 women were diagnosed with CRC [2], and 113,200 men and 101,500 women died from CRC (41). In the USA, 136,830 cases newly diagnosed with CRC and 50,310 deaths with CRC were projected in 2014 (42).

Despite recent developments in targeted therapies, gene sequencing and molecular diagnostics, promising optimized and personalized treatment regimens tailored for individual patients, CRC remains one of the less treatable cancers. Most cases of CRC are sporadic and develop slowly over several years, progressing through a series of clinical and histopathological stages from single crypt lesions through benign adenomas to malignant carcinomas, as a result of an accumulation of mutations in tumour suppressor genes and oncogenes or a genetic instability (43, 44). The 5-year survival rate for early-stage CRC is about 90% but it falls to 10% for late-stage CRC metastasized to distant sites (45) and cancer mortality is mainly due to metastasis (46, 47).

There are multiple treatments available for patients with metastatic colorectal cancer (mCRC), including targeted therapies guided by biomarkers (48-50). Recent advances in targeted therapies have raised expectations that clinical application of biomarkers might improve health benefits while avoiding unnecessary toxicity and adverse events. It can potentially reduce health care system costs by containing unnecessary costs without hurting patient health outcomes (51).

These therapies comprise epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), and tyrosine kinase (TK) inhibitors. VEGF-targeted therapies include bevacizumab, aflibercept, and ramucirumab. EGFR inhibitors are cetuximab and panitumumab. Regorafenib is a TK inhibitor. Of these, only anti-EGFR therapies have a predictive biomarker clearly established for guiding treatment options as an integral part of the clinical pathways (52, 53). Current guidelines in Europe and the USA recommend that all mCRC patients receive Kirsten rat sarcoma (KRAS) testing prior to treatment with EGFR inhibitors since KRAS mutation status – wild type (WT) or mutant (MT) – predicts the response to anti-EGFR therapies (54, 55). Recently, the testing was expanded to RAS

testing (both KRAS and NRAS) (56). KRAS and NRAS mutations serve as predictive biomarkers for anti-EGFR therapies, only patients with RAS wild-type tumours benefit from these therapies. No positive predictive biomarkers exist yet, that identify eligible patients rather than exclude ineligible patients. No other molecular marker is part of routine clinical practice when deciding optimized and tailored treatment regimens for mCRC patients. However, irinotecan is a biomarker-directed chemotherapy for treating mCRC, which unlike molecularly targeted therapies, is a cytotoxic drug given to get rid of or control cancer cells. UGT1A1 testing showed clinical benefits for the administration of irinotecan (57). All these predictive biomarkers are currently used in clinical settings to make treatment decisions for the safe and effective use of targeted therapies in treating mCRC.

Third-party payers often prioritize competing interventions by assessing cost-effectiveness using cost-effectiveness (CEA) and cost-utility analysis (CUA) (3). The former is often assessed per additional life-years gained (LYs), and the latter per additional quality-adjusted life-year (QALY). Incremental differences in costs and benefits between alternative interventions are the main focus of economic evaluations and thus, the primary study outcome is usually to estimate the incremental cost-effectiveness ratio (ICER) per LYs or QALYs (3). The comparison of alternative courses of action for cancer biomarkers for targeted therapies can be broadly categorised into two forms: 'test-treat' strategy (patients are treated with new intervention guided by biomarker status) and 'treat-all' strategy (all patients are treated without biomarker testing) (58).

To sum up, the use of biomarkers may permit optimising regimens without compromising health outcomes. This has significant implications for healthcare payers in containing expenditures that provide no or minimal benefits to patients. Despite such high expectations, the cost-effectiveness of cancer biomarkers remains unclear given that they

are often co-assessed as part of high cost targeted therapy. This study systematically reviews economic evaluations of biomarker-guided therapies and aims to determine the impact of companion biomarkers on the cost-effectiveness of the corresponding therapies in mCRC.

MATERIALS AND METHODS

Literature search

A systematic literature search on the cost-effectiveness of cancer biomarkers for targeted therapies in mCRC was performed using Medline (Ovid), Embase (Ovid), EconLit, and the National Health Service Economic Evaluation Database (NHSEED) in June 2018. The search terms (**Error! Reference source not found.** 2-1) were validated by an information specialist. The reference lists of relevant articles were scrutinized, and the grey literature was hand-searched.

The electronic search was performed using Medical subject heading (MeSH) terms and keywords that were developed based on patients (mCRC), intervention (cancer biomarkers for targeted therapies), and outcome (ICERs). These were combined with free-word texts using relevant economic terms (e.g. “cost-effectiveness”) and the drug names of targeted therapies both in brand and generic terms. Targeted therapies granted a marketing authorization with companion biomarkers by the European Medicines Agency (EMA) or US Food and Drug Administration (FDA) were included in the literature search strategy (52). Studies published in English were searched from 2000 until June 2018.

Study selection

The study selection was based on the inclusion and exclusion criteria formulated by the PICOS framework i.e., population, intervention, comparator, outcome, study type (Appendix 2-2). Given the companion nature of predictive biomarkers for targeted therapies, their cost-effectiveness is interconnected with clinical effectiveness and costs of corresponding therapies as well as biomarker tests. Hence, the cost-effectiveness of biomarker testing as well as corresponding agents were included in this review. Selection of papers followed the eligibility criteria below:

- Population: the intervention is being applied to adult patients with a diagnosis of mCRC.
- Intervention: cancer biomarkers for targeted therapies (predictive/companion biomarkers). These biomarkers are used as diagnostic tools to guide treatment or select patients responsive to subsequent corresponding therapies. Cancer biomarkers without market authorizations co-licensed with targeted therapies were excluded.
- Comparator: conventional treatments or targeted therapies with or without use of biomarker tests.
- Outcome: ICERs for LYs, ICERs for QALYs. Studies merely reporting costs or effectiveness were excluded.
- Study type: economic evaluations including model or trial-based analyses. Studies merely reporting on methodological issues, reviews, comments, letters or editorials were excluded.

The study selection had three main stages. Firstly, search hits from the electronic databases were imported into EndNote and duplicate citations were removed. Secondly,

the titles and abstracts of the identified articles were screened independently by two reviewers. Studies clearly indicated as irrelevant were excluded. Thirdly, the full articles retrieved that met the inclusion criteria were screened by two reviewers, with any disagreements between reviewers resolved by discussion.

Data extraction

A data extraction form was created based on the Cochrane Handbook of Systematic Reviews of Interventions and the CHEERS statement (38, 59). The following items were extracted: publication details, target patients, interventions, comparators, outcomes (ICERs), study designs. Data extraction was performed by the first assessor (MKS) using Microsoft Excel® and any ambiguities were resolved by discussion with the second reviewer (JC).

Quality assessment

The methodological quality of the included studies was assessed using the Quality of Health Economic Studies (QHES) scales (60). The QHES has been validated and shown to be useful in discriminating higher quality economic evaluation studies from poorer ones (61). The quality assessment was conducted by two assessors (MKS, JC). Since no standardized interpretation of QHES scores exist, we assigned QHES scores to three quality groups; above 70 scores as high quality, between 50 and 70 as fair quality, and below 50 as poor-quality studies. Final QHES score per study was resolved by discussion.

Synthesizing data

The cost-effectiveness results of included studies divided into two groups: 1) the cost-effectiveness of cancer biomarkers for targeted therapies (predictive/companion biomarkers), 2) the cost-effectiveness of targeted therapies licensed with companion biomarkers. ICERs for companion biomarkers are the primary outcome of this study and those for targeted therapies are a secondary outcome.

To enhance the comparability of heterogeneous cost-effectiveness studies especially for the primary outcome of this review, the cost-effectiveness results for companion biomarkers were qualitatively synthesized by the strategies compared in economic evaluations as described below.

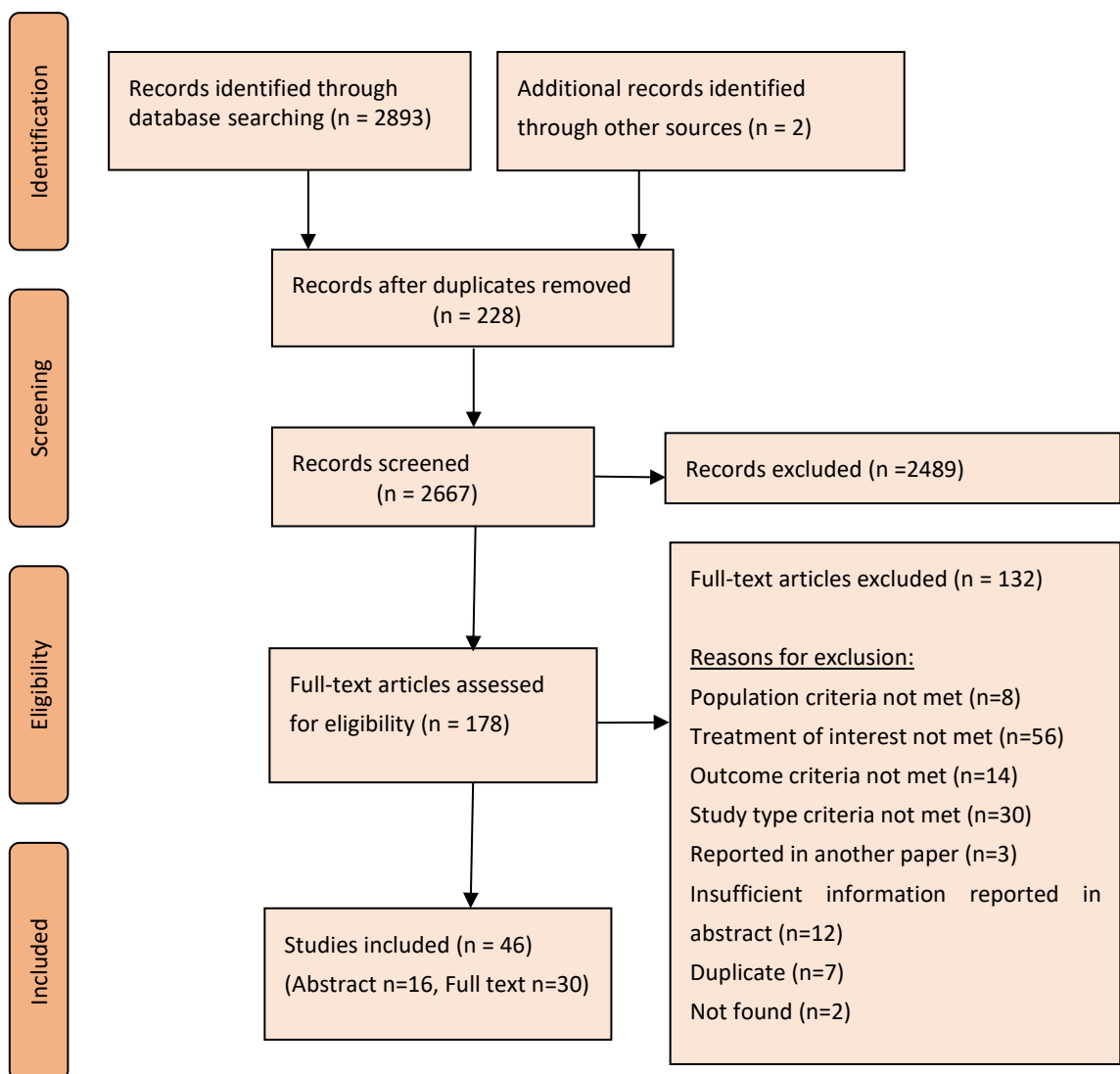
- 1) 'Test-treat' strategy: Biomarker test performed, and therapy guided by the biomarker results; for example, RAS wild-type patients receive new intervention (i.e. targeted therapies) and RAS mutant patients receive standard care (i.e. existing therapies/best supportive care (BSC)/chemotherapy).
- 2) 'Treat-all' with new therapy strategy: No biomarker test performed, and all patients treated with new intervention.
- 3) 'Treat-all' with standard care strategy: No biomarker test performed, all patients treated with standard care.

RESULTS

Literature search and study selection

The electronic search located 2893 publications, and reference tracking identified two additional articles. Duplicates (228 papers) were removed, resulting in 2667 unique studies. The titles and abstracts were then assessed according to the pre-determined eligibility criteria, and 2489 papers were excluded. A total of 178 papers were selected for full-text assessment. Main reasons for exclusion were the type of intervention studied (i.e. not related to cancer biomarkers for targeted therapies) and the study type (i.e. not economic evaluations or cost-effectiveness analyses). Fifteen papers were excluded because the results were reported in another paper or insufficient information was reported in abstract only. Fourteen papers were excluded as they did not report ICERs as their study outcome. Eight papers were additionally excluded because they did not target patients with mCRC. Altogether, 46 publications were included in the review, consisting of 30 studies reported in full text and 16 reported in abstract only. Study selection is presented in a PRISMA flow diagram (Figure 2-1)

FIGURE 2-1 : PRISMA FLOW DIAGRAM OF STUDY SELECTION

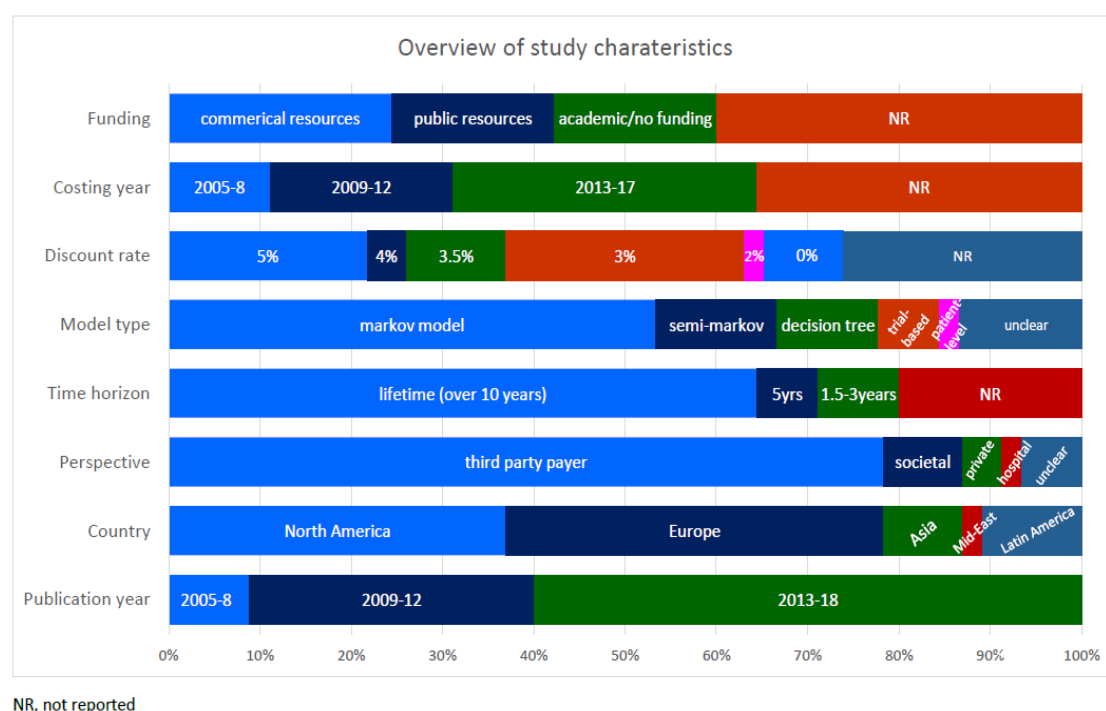


Overview of included studies

The modelling designs, the intervention strategies, and the comparator strategies of the included cost-effectiveness studies were heterogeneous. The majority of studies were model-based economic evaluations except for three trial-based studies. Analyses involved comparisons between two and seven strategy arms. Most studies employed the perspective of third-party payers (79%), while only a small proportion of studies adopted a societal perspective (8%) and patient or hospital perspectives. The type of perspective

was not disclosed in three studies (62-64). Most of the included studies were modelled for lifetime or more than 10-year time horizons (66%), while trial-based analyses were modelled only for their trial periods, i.e. 1.5 or 2 years. Most of the studies were set in Europe (40%) and North America (35%), except for six in Latin America, five in Asia, and one in the Middle East. Manufacturer sponsorship was declared by 13 studies, while most studies were either funded by public or academic resources (nine studies from public resources, eight studies from either academic resources or no external funding). Most abstracts did not declare funding source for their projects. Moreover, three full papers did not declare their source of funding. Study characteristics are synthesized in Figure 2-2 and detailed characteristics for each study are provided in Appendix 2-3. No economic evaluations of cancer biomarkers for targeted therapies in mCRC were published before 2005. Many studies were published in recent years, 60% after 2012. Four studies appeared between 2005-08, 14 studies in 2009-12, and 28 studies in 2013-18. Likewise, recent years were used in costing years of assessments; the years of 2005-08 in five studies, 2009-12 in nine studies, and 2013-18 in sixteen studies. However, a considerable number of assessments did not specify a base year for pricing (17 studies).

FIGURE 2-2 : OVERVIEW OF STUDY CHARACTERISTICS



Primary synthesis

- ***Cost-effectiveness of predictive biomarkers in mCRC***

Seventeen studies investigated the cost-effectiveness of cancer biomarkers for targeted therapies (Tables 2-1, 2-2, 2-3) (detailed results of ICERs per study are provided in Appendix 2-4. These studies assessed the cost-effectiveness of predictive (companion) biomarkers aside from that of the corresponding therapies. Overall, all studies showed favourable results toward predictive biomarkers. Thirteen studies found biomarker testing to be cost-effective (30, 65-76), of which four studies reported biomarker testing to be dominant (30, 70-72). Five studies showed cost-saving (77-81) compared to that of 'no-testing'. Wen et al. (69) evaluated cost-effectiveness of RAS screening prior to monoclonal antibodies and found that RAS testing before cetuximab is more cost-effective compared to KRAS-testing with cetuximab. After re-calculating their ICERs, we concluded that all strategies they used

were well beyond the acceptable willingness to pay thresholds in China, but RAS testing appeared to be more favourable than KRAS testing for patients with mCRC. Some studies reported conflicting results of cost-effectiveness between predictive biomarkers and corresponding therapies; the biomarkers were cost-effective, but their corresponding therapies were not (71, 77-79). Existing predictive biomarkers (or companion diagnostics) co-licensed with targeted therapies in mCRC included KRAS and RAS approved for the use of panitumumab and cetuximab, and UGT1A1 genotyping approved for the administration of irinotecan. KRAS and RAS testing was the most frequently evaluated in economic evaluations (KRAS testing in eight studies; RAS testing in seven studies) and UGT1A1 testing in four studies.

- ***Cost-effectiveness of KRAS testing***

All studies reported favourable cost-effectiveness for KRAS testing prior to the administration of the corresponding targeted therapies, while four corresponding therapies were not cost-effective (Table 2-1). KRAS testing for targeted therapies was assessed mostly to pre-select eligible patients before administering EGFR therapies such as cetuximab or panitumumab. As shown in Table 7, all studies suggested favourable cost-effectiveness for the use of KRAS testing in administering EGFR therapies. Although 50% of these studies reported the corresponding targeted therapies as not cost-effective (71, 77-79), they found that KRAS testing was cost-effective (n=4) or at least cost-saving (n=4) prior to the provision of corresponding therapies.

TABLE 2-1 : COST-EFFECTIVENESS FINDING OF KRAS TESTING FOR CORRESPONDING TARGETED THERAPIES

Study	Strategy comparison	Model type, time horizon	ICER/LYs (re-calculated if necessary)	ICER/QALYs (re-calculated if necessary)	Currency, year	Conclusion based on outcome
<i>'Test-treat' strategy compared to 'treat-all' patients with standard care without testing</i>						
Behl et al. 2012 (77)	KRAS testing plus Cmab vs. Treat all with BSC	Markov model, 10-year	672,216*	NA	US\$, 2010	The use of KRAS testing was cost-saving prior to Cmab however, Cmab plus KRAS testing was not cost-effective.
Blank et al. 2011 (65)	KRAS testing plus Cmab vs. Treat all with BSC	Markov model, Lifetime	NA	63,647*	Euro, NR	KRAS testing prior to Cmab is clinically appropriate and economically favorable.
Carlson J.J. 2010 (78)	KRAS testing plus Cmab vs. Treat all with BSC	Decision analytic model, NR	NA	264,644	US\$, NR	KRAS testing was cost-saving but Cmab plus KRAS testing was not cost-effective.
Health Quality Ontario 2010 (66)	KRAS testing plus Cmab vs. Treat all with BSC	Markov model, Lifetime	NA	54,802	CA\$, 2009	KRAS testing was cost-effective for all strategies considered.
	KRAS testing plus Pmab vs. Treat all with BSC		NA	47,795	CA\$, 2009	
	KRAS testing plus Cmab + Irinotecan vs. Treat all with BSC		NA	42,710	CA\$, 2009	
Shiroiwa et al. 2010 (71)	KRAS testing plus Cmab vs. No-KRAS testing (Treat all with BSC)	Markov model, 2.5- years	120,000	180,000	US\$, 2010	KRAS testing strategy was dominant compared to no-KRAS testing strategy. However, Cmab (with or without KRAS testing) was not cost-effective.
<i>'Test-treat' strategy compared to 'treat-all' patients with new treatment without testing</i>						

Niedersuess-Beke D. et al. 2015 (80)	KRAS testing + Pmab or Cmab vs. No predictive biomarker testing (Cmab/Pmab all)	NR, NR	26,276	NA	EU€, 2013	Testing predictive biomarkers is cost-saving.
<i>'Treat-all' patients with new treatment without testing compared to 'test-treat' strategy</i>						
Behl et al. 2012 (77)	Treat all with Cmab vs. KRAS testing plus Cmab	Markov model, 10-years	2,932,767	NA	US\$, 2010	Treating all patients with Cmab without testing was not cost-effective; no-testing is not cost-effective.
Blank et al. 2011 (65)	Treat all with Cmab vs. KRAS testing plus Cmab	Markov model, Lifetime	NA	314,588	Euro, NR	Treating all patients with Cmab without testing was not cost-effective.
Health Quality Ontario 2010 (66)	Treat all with Cmab vs. KRAS testing plus Cmab	Markov model, Lifetime	NA	Dominated	CA\$, 2009	No-testing was not cost-effective.
	Treat all with Cmab vs. KRAS testing plus Pmab		NA	308,236	CA\$, 2009	
	Treat all with Cmab vs. KRAS testing plus Cmab + Irinotecan		NA	163,396	CA\$, 2009	
Vijayaraghavan et al. 2012 (30)	Treat all with Cmab/Pmab/Combination therapy vs. KRAS testing plus Cmab/Pmab/Combination therapy	Markov model, Lifetime	Higher costs, same effectiveness	NA	US\$, 2009; EU€ 2009	No-testing was not cost-effective (dominated).
<i>Pre-defined genetic population (KRAS WT patients)</i>						
Harty et al. 2015 (79)	Cmab + FOLFIRI vs. FOLFIRI; strategies compared between different cohorts of patients stratified by different biomarker status including KRAS WT group	NR, NR	NA	72,053	GB£, NR	Cmab plus chemotherapy was not cost-effective in a subgroup of patients with KRAS WT. However, the stratification of patients by genetic biomarker status does improve the cost-effectiveness of corresponding therapies.

*ICERs were re-calculated using total costs and effects provided in the pertinent paper.

AB; abstract, NA; not available, NR; not reported.

Although all studies suggested favourable cost-effectiveness of KRAS testing before providing EGFR therapies, the inclusion of KRAS biomarker testing did not necessarily ensure the cost-effectiveness of the costly corresponding targeted therapies. For example, Behl et al. (77) evaluated the cost-effectiveness of KRAS testing to select patients responsive to cetuximab compared to administering cetuximab to all patients without testing. We re-calculated their ICERs in order to evaluate cost-effectiveness using an appropriate strategy comparison such as 'test-treat' strategy against 'treating all patients with BSC without testing' strategy. KRAS testing plus administering cetuximab had a lower ICER (\$672,216) than treating all patients with cetuximab with no KRAS testing (\$827,913), when both strategies were compared against the reference strategy of not providing cetuximab at all. It confirms that KRAS testing saved some costs by restricting cetuximab to particular patients, however cetuximab is yet far beyond the acceptable cost-effectiveness thresholds of USA.

Carlson (78) compared two intervention strategies (1. Cetuximab for all patients, 2. Cetuximab for KRAS wild-type and BSC for KRAS mutant patients based on biomarker testing) compared to BSC for all patients without biomarker testing. Neither intervention strategy was cost-effective. However, the KRAS testing strategy saved \$10,037 with a negligible decrease in QALYs compared to the cetuximab for all-patients strategy. Likewise, Shirowa and colleagues (71) conducted a comparative analysis using the same strategies; 1) KRAS-testing strategy, 2) No KRAS-testing strategy (cetuximab for all), 3) No cetuximab strategy (BSC for all). They found the KRAS-testing strategy dominated the no-KRAS-testing (cetuximab for all) strategy, however, the ICER for cetuximab (with or without KRAS testing) was too high even if treatments were limited to KRAS wild-type patients. Meanwhile, Harty and colleagues (79) investigated the cost-effectiveness of cetuximab in combination with irinotecan when patients were stratified into different genetic biomarker groups and

suggested that the use of a biomarker improved the cost-effectiveness of cetuximab but its ICER was beyond acceptable thresholds for UK.

To sum up, targeted therapies were never cost-effective when a 'no-testing strategy (treating all patients with new therapy)' was compared to a 'test-treat' strategy. This confirms that KRAS testing is a better use of resources than 'no-testing' prior to the administration of targeted therapies. However, when a 'test-treat' strategy was compared to 'treat all with BSC/SOC', there were conflicting results; three studies not cost-effective (71, 77, 78) and two studies favourable (65, 66). This implies a positive impact of KRAS testing in improving the cost-effectiveness of its companion therapies however; it does not necessarily mean that KRAS testing can ensure the cost-effectiveness of subsequent targeted therapy.

- ***Cost-effectiveness of RAS testing***

Seven studies evaluated the cost-effectiveness of RAS testing and most of them found favourable results for RAS biomarker testing (Table 2-2). Of these, two studies assessed the cost-effectiveness of RAS screening compared with that of KRAS testing with targeted therapies (69, 72). Both studies were performed from a Chinese health care system perspective and found that RAS testing was cost-effective compared to KRAS testing with cetuximab. However, Wu et al. (76) found that RAS testing with cetuximab is only cost-effective when a patient assistance programme is available in China. However, Wen et al. (69) found that bevacizumab with RAS testing was not cost-effective compared to bevacizumab with KRAS testing. They reported \$74,600 which is far more than three times Chinese GDP per capita (\$24,000 (82)).

TABLE 2-2 : COST-EFFECTIVENESS FINDING OF RAS TESTING FOR CORRESPONDING TARGETED THERAPIES

Study	Comparison	Model type, time horizon	ICER/LYs (re-calculated if necessary)	ICER/QALYs (re-calculated if necessary)	Currency, year	Conclusion based on outcome
<i>'Test-treat' strategy compared to 'treat-all' patients with standard care without testing</i>						
Wu et al. (76)	Cmab + FOLFIRI vs. FOLFIRI	Markov model, 10-year	12,107	\$14,049	US\$, 2016	RAS testing with Cmab is cost-effective when patient assistance program is available in China.
<i>'Test-treat' strategy compared to 'treat-all' patients with new treatment without testing</i>						
Niedersuess-Beke D. et al. 2015 (80)	RAS testing + Pmab or Cmab vs. No predictive biomarker testing (Cmab/Pmab all)	NR, NR	9,686	NA	EU€, 2013	Predictive biomarker testing was cost-saving; RAS testing scenario showed lower ICERs than KRAS testing scenario.
Saito et al. 2017 (68)	RAS testing vs. No testing before EGFR therapies	Markov model, 5-year	2,574,111	3,049,132	JP¥, NR	RAS testing was cost-effective compared to no-testing; however, comprehensive profiling is more cost-effective than RAS testing only.
<i>Pre-defined genetic population (RAS WT patients)</i>						
Harty et al. 2015 (79)	Cmab + FOLFIRI vs. FOLFIRI for patients stratified into RAS WT group	NR, NR	NA	44,184	GB£, NR	Stratification of patients by genetic biomarker status improved cost-effectiveness of Cmab; however, its ICERs was yet beyond the £20,000-£30,000 thresholds for UK. Recently however, NICE committees accepted that it was a life-extending end-of-life treatment and approved under the exceptional thresholds of £50,000 in UK(83).
Souza et al. 2017 (75)	Cmab + Chemotherapy vs. Chemotherapy alone	Markov model, 20-year	NA	56,750	BRL\$, NR	The addition of Cmab to the standard chemotherapy is a cost-effective therapy for RAS WT patients with liver-limited disease.

Wen et al. 2015 (69)	RAS-Cmab vs. KRAS-Cmab	Markov model, 10- years	NA	17710*	US\$, 2014	Patients treated with Cmab and RAS-testing was more cost-effective against the strategy of KRAS-testing and treated with Cmab.
	RAS-Bmab vs. KRAS-Bmab		NA	71079*		Patients with RAS-testing and treated with Bmab was not cost-effective compared to KRAS testing and treated with Bmab.
Zhou et al. 2016 (72)	RAS-Cmab vs. KRAS-Cmab	Markov model, Lifetime	NA	(22450)*	US\$, NR (2016 assumed)	RAS screening was dominant over KRAS testing.
	RAS-Bmab vs. KRAS-Bmab		NA	(3966)*		

*ICERs were re-calculated using total costs and effects provided in the pertinent paper.

AB; abstract, NA; not available, NR; not reported.

However, most of these studies did not use an appropriate strategy comparison such as evaluating a 'test-treat' strategy in comparison to a 'treat all with existing standard therapy'. Two studies were compared against 'treat all with new therapy', and four studies were performed in a pre-defined genetic population. Only one recent study employed a comparative strategy of chemotherapy alone without mutation testing (76), however, this economic evaluation was of relatively low quality. Thus, the evidence on cost-effectiveness of RAS testing is still inconclusive. Further evaluation is required using an appropriate comparator strategy of 'treat all patients with standard care without testing' instead of 'treating all with new therapy without testing'.

- ***Cost-effectiveness of UGT1A1 testing***

The four studies assessing UGT1A1 genotyping for the administration of irinotecan found that the genotyping was either cost-saving or cost-effective (Table 2-3). However, Obradovic et al. (81) reported that UGT1A1 genotyping in combination with a reduced dose of irinotecan was not cost-effective for Asian population groups, reporting very high ICERs at \$6,818,000. Since all studies were conducted for populations in Europe or USA, further research on Asian populations to confirm this difference in cost-effectiveness of UGT1A1 testing may be required before deciding to reduce irinotecan doses.

TABLE 2-3 : COST-EFFECTIVENESS OF UGT1A1 TESTING

Study	Comparison	Model type, time horizon	ICER/LYs (re-calculated if necessary)	ICER/QALYs (re-calculated if necessary)	Currency, year	Conclusion based on outcome
<i>'Test-treat' strategy versus 'treat all' patients with standard care without testing</i>						
Butzke 2016 (70)	UGT1A1 genotyping and dose reduction vs. the current standard of no testing	Markov model, Lifetime	NA	Dominant	EU€, 2013	UGT1A1 testing dominates the strategy of no-testing strategy in treating patients with irinotecan-based chemotherapy.
Gold et al. 2009 (73)	UGT1A1 testing and dose reduction of irinotecan vs. the current standard of no testing	Decision-analytic model, 5-year	NA	Favorable	US\$, 2007	UGT1A1 testing could be cost-effective if irinotecan dose reduction does not reduce efficacy.
Obradovic et al. 2008 (81)	UGT1A1 testing and dose reduction of irinotecan vs. No UGT1A1 testing and standard care of irinotecan	Decision analytic model, Lifetime	Cost-saving (African, Caucasian)	NA	US\$, 2006	Genotyping with dose reduction of irinotecan was cost-saving for the population of African/Caucasian however, not cost-effective for Asian populations.
			6,818,203 (Asian)	NA		
Pichereau et al. 2010 (67)	UGT1A1 genotyping before irinotecan vs. no genotyping strategy	Decision tree, Lifetime	942.8 - 1090.1	NA	EU€, 2006	Genotyping strategy was cost-effective compared to no-testing strategy.

NA; not available or not applicable

All studies compared alternative strategies correctly, between ‘test-treat’ with new intervention and ‘treat all’ patients with standard care without testing. For example, Gold and colleagues (73) assessed the comparative analysis of UGT1A1 testing and no testing prior to irinotecan administration, using different scenarios of dose reduction efficacy of irinotecan. They reported that, assuming no reduction in treatment efficacy, the average cost savings of the genotyping test were \$272.34 with 0.073 quality-adjusted days saved. Most recently, Butzke et al. (70) evaluated the UGT1A1 genotyping from a German statutory health insurance perspective and found that genotyping prior to irinotecan-based chemotherapy dominates non-guided colon cancer care in Germany. However, this study also reported that there is substantial structural uncertainty in relation to the degree of dose-reduction in heterozygotic patients and suggested to validate it in clinical practice whether physicians indeed chose to reduce dosing in both heterozygote and homozygote patients.

Overall, UGT1A1 testing appears to be cost-effective prior to the administration of irinotecan, especially in relation to dose reduction and prevention of adverse events. However, two studies used narrow health outcome measures such as neutropenia avoided (67, 81) and one study suggested a conditional cost-effectiveness of UGT1A1 testing depending on the treatment efficacy of irinotecan dose reduction.

Secondary synthesis

- ***Cost-effectiveness of targeted therapies licensed with companion biomarkers***

In 29 studies, the cost-effectiveness of targeted therapies was evaluated (62-64, 84-96). This secondary synthesis analyses economic evaluations of targeted therapies which did

not explicitly analyse the value of predictive biomarkers as part of assessing the cost-effectiveness of biomarker-guided therapies. Fifty-nine percent of these economic evaluations reported favourable cost-effectiveness findings for targeted therapies licensed with companion biomarkers in treating mCRC (n=17). 41% reported that targeted therapies were not cost-effective (n=12).

76% of these studies (n=22) performed their comparative analyses in a pre-defined genetic population such as biomarker-positive patients and often, no differences in the value of predictive biomarkers were modelled. These studies frequently assumed that the study population (in all strategy arms) was tested before entering the economic models. However, all studies related to UGT1A1 testing considered the intrinsic value of UGT1A1 testing as an integral part of their comparative analysis in administering irinotecan-based chemotherapies. Among the remaining seven studies, treatment decisions in four studies (62, 84, 97, 98) depended on biomarker mutational status, but in three studies (99-101) the comparative strategies employed were not clear.

Overall, this secondary synthesis found that the inclusion of predictive biomarkers improved the cost-effectiveness of targeted therapies, but the improvement was insufficient to make the corresponding targeted therapies cost-effective. It may imply that the impact of their high drug costs on the cost-effectiveness of targeted therapies is much greater than that of the health benefits gained from pre-selection of responsive patients guided by biomarkers.

Table 2-4 presents the cost-effectiveness results for targeted therapies labelled with predictive biomarkers (the ICERs are reported in). In the case of bevacizumab, which has not yet an established biomarker in clinical settings, it was often assessed as a comparator strategy (n=8) and not often as an intervention strategy. But two studies compared all

three therapies (cetuximab, panitumumab and bevacizumab) and found bevacizumab to be cost-effective (102, 103). Both studies were conducted in a pre-defined group of patients with KRAS wild-type status. All 29 studies included either cetuximab or panitumumab in their comparative assessments.

TABLE 2-4 : COST-EFFECTIVENESS OF TARGETED THERAPIES LICENSED WITH COMPANION BIOMARKERS

Study	Treatments/Strategies	Model type, time horizon	Biomarker test	Outcome measure	Conclusion based on outcome
Annemans et al. 2007 (84)	1. Cmam + Irinotecan (6 week rule, 12 week rule) 2. Current treatment	Trial-based model, NR	NS	LYs	Cmam + Irinotecan is cost-effective in Belgium.
Asseburg et al. 2011 (85)	1. Cmam + FOLFIRI 2. Bmam + FOLFOX	Patient-level simulation, 10-year	KRAS	LYs	First line treatment with Cmam plus FOLFIRI offers a cost-effective treatment option versus Bmam plus FOLFOX for KRAS WT genotype patients in Germany. Thus, KRAS testing should be performed on all presenting cases of mCRC to ensure access to this treatment option.
Carvalho et al. 2017 (104)	1. Pmam 2. Cmam 3. BSC	Markov model, Lifetime	RAS	LYs	Both Pmam and Cmam are not cost-effective in patients with RAS WT mCRC.
Chaugule et al. 2012 (105)	1. Cmam + BSC 2. BSC alone	Markov model, Lifetime	KRAS	QALYs	Cmam is not cost-effective in KRAS WT patients with mCRC.
Davari et al. 2015 (99)	1. FOLFIRI, FOLFOX, CAPOX without the addition of Cmam 2. FOLFIRI, FOLFOX, CAPOX with the addition of Cmam	Unclear, NR	KRAS	LYs, QALYs	Addition of Cmam to FOLFIRI, FOLFOX, CAPOX (Capecitabin+oxaliplatin) is not cost effective.
Dos Santos et al. 2015 (86)	1. Pmam + mFOLFOX6 2. Bmam + mFOLFOX6	Markov model, Lifetime	RAS	LYs, QALYs	Pmam is clearly cost-effective compared to Bmam for treatment of wild-type RAS mCRC in Brazil.
Ewara et al. 2014 (102)	1. Bmam + FOLFIRI 2. Cmam + FOLFIRI 3. Pmam + FOLFIRI	Markov model, Lifetime	KRAS	QALYs	Bmam+FOLFIRI is cost-effective. Bmam + FOLFIRI found to be dominant over the other two strategies. The other two strategies are dominated by Bmam + FOLFIRI. However, sensitivity analysis

					showed that Cmab + FOLFIRI is being cost-effective under certain range of parameter values - thus, further investigation needed for Cmab.
Graham et al. 2014 (87)	1. Pmab 2. Bmab	Semi-Markov model, Lifetime	KRAS, RAS	LYs, QALYs	Pmab plus mFOLFOX represents good value for money compared to a current SOC Bmab plus mFOLFOX6.
Graham et al. 2016 (88)	1. Panitumumab in pts with KRAS WT status 2. Cetuximab in pts with KRAS WT status	Semi-Markov model, Lifetime	KRAS	LYs, QALYs	Compared to Cmab, the study suggested that Pmab is favorable.
Hnoosh et al. 2015 (AWMSG) (89)	1. Cmab + either FOLFOX, FOLFIRI, CAPOX 2. FOLFOX 3. FOLFIRI 4. CAPOX	Markov model, 10-year	RAS	QALYs	Cmab is cost-effective and a good use of NHS Wales resource through stratification of RAS WT patients.
Hnoosh et al. 2015 (NICE) (106)	1. Cmab + either FOLFOX, FOLFIRI, CAPOX 2. FOLFOX 3. FOLFIRI	Markov model, 10-year	RAS	QALYs	Cost-effectiveness of Cmab could be deemed favorable when considering it as end-of-life medicine.
Hoyle et al. 2013 (97)	1. Cmab 2. Cmab + Irinotecan 3. Pmab 4. BSC	Semi-Markov model, 10 years (lifetime)	KRAS	LYs, QALYs	All three strategies (Cmab, Cmab+Irinotecan, Pmab) are not cost-effective.
Huxley et al. 2017 (98)	1. FOLFOX (reference strategy) 2. Cmab + FOLFOX 3. Pmab + FOLFOX	Semi-Markov model, 30 years (lifetime)	RAS	QALYs	Cmab and Pmab in combination with chemotherapy are likely to be poor value for money.

Junqueira et al. 2015 (RAS subgroup) (90)	1. Cmab + FOLFIRI 2. FOLFIRI	Markov model, 10 years	RAS	LYs	Cmab+FOLFIRI is cost-effective for a subgroup of patients with RAS wild-type.
Junqueira et al. 2015 (Cmab and Bmab) (91)	1.Cmab+FOLFIRI 2.Bmab+FOLFIRI	Markov model, 10 years	RAS	LYs	The use of Cmab shown significant and meaningful benefits while being cost-saving to HCS in Brazil.
Kourlaba et al. 2014 (92)	1. Pmab + FOLFOX6 2. Bmab + FOLFOX6	Markov model, NR	RAS	QALYs	Pmab + mFOLFOX6 is cost-effective.
Krol et al. 2015 (107)	1. Cmab + FOLFIRI 2. FOLFIRI 3. Cmab + FOLFOX 4. FOLFOX	Markov model, 20-year	RAS	QALYs	ICUR results were close to CET. ICURs strongly differed from the Netherlands and Belgium. It is mainly due to lower drug costs in Belgium.
Lawrence et al. 2013 (103)	1. FBC (reference) 2. Bmab + FBC 3. Cmab + FBC 4. Pmab + FBC	Markov model, Lifetime (to maximum of 10 years)	KRAS	QALYs	Bmab + FBC offers the best value for money in KRAS WT patient population.
Mittmann 2009 (108)	1. Cmab + BSC 2. BSC	Trial-based model, Duration of the clinical trial (18-19 months)	KRAS	LYs, QALYs	ICER of Cmab over BSC alone for unselected mCRC pts was high and sensitive to drug costs. ICER was lower when the analysis was limited to pts with KRAS WT.
Moreno et al. 2012 (62)	1. Scenario A: KRAS WT pts receive weekly Cmab + FOLFOX 2. Scenario B. Pmab + FOLFOX 3. Scenario C. Cmab biweekly + FOLFOX	Unclear, NR	KRAS	Response rate	1st line oxaplatin combinations of biweekly Cmab for WT and Bmab for MT optimize cost per additional response rate rather than Pmab-based schedules.

Norum J. 2006 (100)	1. 3rd line chemotherapy (Cmab + Irinotecan) 2. No 3rd line chemotherapy	Decision tree, Unclear	EGFR	LYs	Cmab + Irinotecan as 3rd line therapy in mCRC is promising, but a very expensive antibody. Reduced drug cost and/or improved overall survival may alter this conclusion.
Ortendahl et al. 2014 (63)	1. FOLFIRI + Cmab 2. FOLFIRI + Bmab	Unclear, Lifetime	KRAS, RAS	LYs, QALYs	Cmab + FOLFIRI improve health outcomes and use financial resource more efficiently compared to Bmab + FOLFIRI.
Riesco-Martinez 2016 (109)	Strategy 1 (reference strategy: EGFR monotherapy in 3rd line). Strategy 2 (EGFR and Irinotecan in 3L). Strategy 3 (EGFR in 1L).	Markov model, 5-year	KRAS, RAS	QALYs	1st line of EGFR is not cost-effective at its current pricing relative to Bmab.
Rivera et al. 2017 (93)	1. Pmab + mFOLFOX6 2. Bmab + mFOLFOX6	Semi-Markov model, Lifetime	RAS	LYs, QALYs	Pmab+mFOLFOX6 is more cost-effective than Bmab+mFOLFOX6 for the first line treatment of RAS WT mCRC.
Samyshkin et al. 2011 (94)	1. Bmab + Chemotherapy 2. Cmab + Chemotherapy 3. Pmab + Chemotherapy	semi-Markov model, Lifetime	KRAS	QALYs	Cmab plus FOLFIRI is the most cost-effective for patients with KRAS WT tumors. ICERs of Cmab + Chemotherapy (CT), Bmab + CT, and Pmab + CT are within the commonly accepted threshold of CE in UK.
Shankaran et al. 2015 (95)	1. FOLFIRI plus Cmab in treatment-naïve patients with KRAS wt type in mCRC 2. FOLFIRI plus Bmab treatment-naïve patients with KRAS wt type in mCRC	Decision tree, 2 years (trial period)	KRAS, RAS	LYs, QALYs	Results were more favorable for Cmab in RAS-WT patients.
Starling et al. 2007 (101)	1. Cmab + Irinotecan 2. Active/best supportive care (ASC/BSC)	Trial-based model, Lifetime	EGFR	LYs, QALYs	ICERs for Cmab+Irinotecan is relatively high compared to other healthcare interventions.
Vargas-Valencia et al. 2015 (64)	1. Pmab + FOLFOX 2. Cmab + FOLFIRI	Markov model, Lifetime	RAS	LYs	Pmab showed treatment outcomes improvement vs. Cmab for RAS WT patients at a lower cost per life year.
Xu et al. 2016 (96)	1. Pmab 2. Cmab	Markov model, 3-year	NR	LYs, QALYs	Pmab dominates over Cmab. Pmab has a cost advantage over Cmab.

AB; abstract, ASC/BSC; active/best supportive care, Bmab; bevacizumab, Cmab; cetuximab, Pmab; panitumumab and NR; not reported

Cetuximab was assessed in the most studies (n=24). More studies found cetuximab not to be cost-effective (14 versus 10 studies finding it cost-effective). Among the studies reporting cetuximab as cost-effective, seven studies (78%) were conducted in a pre-defined genetic population either KRAS wild-type or RAS wild-type, and two not (62, 84). Moreno and colleagues (62) evaluated weekly and biweekly administration of cetuximab compared to panitumumab, where patients in both arms receive biomarker-guided therapies (either cetuximab or panitumumab) when KRAS wild-type and receive bevacizumab when KRAS mutant. They found that biweekly cetuximab for KRAS wild-type and bevacizumab for patients with KRAS mutant status more cost-effective compared to panitumumab-based schedules. Annemans et al. (84) assessed the cost-effectiveness of cetuximab in combination with irinotecan-based chemotherapy compared to current care in Belgium and found that the cetuximab strategy is cost-effective with ICERs between €17000 (6-week treatment scenario) and €40000 (12-week treatment scenario) per LY gained. In this study, all patients in the intervention arm were treated with cetuximab plus irinotecan-based chemotherapy, while patients in the comparator arm were all treated with the current treatment. Nevertheless, none of these studies considered the clinical utility of predictive biomarkers in guiding the optimization of treatments depending on biomarker status in patients.

Among fourteen studies reporting cetuximab as not cost-effective, ten studies were in a pre-defined genetic group and often, this population scoping was used to justify not considering the intrinsic value of predictive biomarkers in the evaluation. Only two studies made the appropriate comparison of a 'test-treat' strategy and a 'treat all with standard of care'. Both were conducted from a perspective of the English NHS and both found cetuximab not cost-effective (97, 98). Hoyle et al. (97) assessed the cost-effectiveness of cetuximab, cetuximab plus irinotecan, and panitumumab for KRAS wild-type patients from

the perspective of the English National Health Service (NHS) and found that all three strategies were not cost-effective compared to BSC. They modelled that 54% of patients were KRAS wild-type and thus, costing £296 per person for KRAS testing (£160 per test). Most recently, Huxley et al. (98) evaluated cetuximab and panitumumab for patients with RAS wild-type mCRC, using a similar comparison structure with Hoyle et al., and they also found that cetuximab and panitumumab in combination of chemotherapy were poor value for money in the English NHS.

Panitumumab assessed in 14 studies, was found to be cost-effective in eight studies (64, 86-88, 92-94, 96) and not cost-effective in six. All studies finding panitumumab to be cost-effective were conducted in a pre-defined genetic group and therefore, further research is required comparing an alternative strategy where all patients receive standard of care without testing rather than that patients in comparator arm are all provided of panitumumab without biomarker testing. For example, two studies reported panitumumab as not cost-effective when compared with treating all patients with best supportive care without prior testing (97, 98).

Bevacizumab was evaluated only in three studies (94, 102, 103), two found it to be cost-effective and one not cost-effective. All three studies were in pre-defined patient groups. Ewara et al. (102) assessed first-line treatment strategies for mCRC patients with KRAS wild-type and compared three strategies of bevacizumab, cetuximab, panitumumab respectively combined with FOLFIRI and found that bevacizumab is dominant over both cetuximab and panitumumab. Similarly, Samyshkin et al. (94) also assessed three strategies of cetuximab, bevacizumab, and panitumumab for the first-line treatments for mCRC patients with KRAS wild-type, however, they found cetuximab plus FOLFIRI is the most cost-effective. But bevacizumab and panitumumab-containing regimens were also

within the acceptable thresholds in UK. On the other hand, Lawrence et al. (103) found bevacizumab was not cost-effective with ICERs of \$131,600 per QALYs, compared to fluoropyrimidine-based chemotherapy (FBC) alone.

Quality assessment

The quality of the included studies was assessed by the Quality of Health Economic Studies (QHES) instrument (Appendix 2-5). The QHES scale consists of 16 weighted questions, with a range of scores from 0 (worst quality) to 100 (best quality). The QHES tool was used by two independent assessors to rate the quality of the studies. QHES score per study is provided in. Economic evaluations reported in full articles were scored using the QHES instrument (n=30) and studies reported only in abstract (n=16) were excluded from quality assessment due to their limited information.

In total, 60% of the studies scored above 70 (good quality) and 33% scored between 50 and 70 (fair quality), and only two papers scored below 50 (low quality). These scores were generated based on 16 'yes or no' questions. The quality elements most commonly omitted from economic evaluations of cancer biomarkers for targeted therapies were the direction and magnitude of potential biases, the methodology for data abstraction, reliable use or justifications of health outcomes measures and scales. For the question "Did the author(s) explicitly discuss direction and magnitude of potential biases?" (Question 14), only 13% of articles were positively rated. With regard to health outcome measures (Question 11), only eight studies got positive scores. As for the question, "Was the methodology of data abstraction (including the value of health states and other benefits) stated?" (Question 7) 43% of articles were scored positively.

The study objectives were clearly presented by all studies (Question 1). The perspective of the analysis was not stated by Behl et al. (77) (Question 2). However, it seems plausible that Behl et al. might have used the perspective of US payer since, they briefly discussed the potential cost savings for the payer, chose the mCRC interventions most commonly used in USA and the analysis was commissioned by US National Institutes of Health. We found eleven papers (67-69, 72, 73, 76, 81, 84, 100, 101, 109) unlikely to have used data from best available source (Question 3). We interpreted this question as meaning that they provided insufficient justification of their choice of data sources. Applying data from another modelling paper or simply using RCT trial data without justifications (i.e. systematic literature review or meta-analysis) was considered insufficient. If estimates came from a subgroup analysis, were the groups pre-specified (Question 4). This item was not applicable for most of the studies since their estimates were not from a subgroup analysis. As for Question 5 on handling uncertainty, we awarded 'yes' to studies which performed at least one type of sensitivity analyses. We found that all studies performed one sensitivity analysis or more. However, five studies (30, 67, 68, 72, 104) only performed one-way sensitivity analysis which may be considered insufficient, for example, the NICE HTA guideline requires probabilistic sensitivity analysis (24). Two studies did not perform incremental analysis between alternatives (Question 6) (30, 69). Many studies did not clearly state the methodology for data abstraction of the values of health states and other benefits (n=17) (Question 7). Four studies did not state the time horizon and discount rates applied in their studies (Question 8) (81, 84, 99, 100). However, some studies justified that they did not discount their costs and benefits because of short time horizon of trial periods (18-19 months or 2 years) (95, 108), however this is not sufficient reason for not discounting and, to be appropriate methodologically, all costs and benefits beyond 1 year need to be discounted. Eight studies (30, 67, 69, 73, 76, 79, 101, 102) did not measure

costs appropriately and the methodology for cost estimation was not clearly described (Question 9). Seven studies (69, 72, 77, 85, 95, 99, 100) did not clearly state primary outcome measures or did not provide clear descriptions of how they were measured (Question 10). Only eight studies (66, 70, 87, 88, 93, 98, 101, 108) used valid health outcomes and provided sufficient justifications for the measures and scales used (Question 11). Most other studies did not provide sufficient information on the health utility measures used or simply borrowed utility values from previous literature without justifications on validity of their measures and scales. Meanwhile, another eight studies did not include health outcomes at all and they estimated ICERs per LYs (30, 67, 77, 81, 84, 85, 100, 104). Four studies were not transparent on their model structure and study methods including how they estimated monetary outcomes of cost-effectiveness (Question 12) (81, 99, 101, 108). For example, Davari et al.(99) provided almost no information about their study methods and modelling structure. Most studies stated the choice of model and assumptions (n=22) (Question 13). However, only four studies discussed potential biases in relation to their study results (70, 98, 100, 102) (Question 14). We found three studies did not come to a reasonable conclusion based on their study results (Question 15) but the conclusions of all other studies appear to be reasonable following their study results. However, three papers implied or suggested the intervention was cost-effective, while it was not cost-effective given the cost-effectiveness thresholds of the respective countries (69, 84, 103). For example, Wen et al. calculated monthly estimations and thus, it should conclude that it is not cost-effective given the yearly WTP in China. All but three studies explicitly disclosed their funding source (66, 68, 84) (Question 16), although the Health Quality Ontario report is likely to be commissioned by public resources (66).

Finally, we also examined if there is any influence of commercial sponsorships in terms of the quality of economic evaluations and found that there is no influence. Among all eighteen studies rated as good quality (≥ 70), ten studies were in fact funded by commercial sources mainly from manufacturers. However, all studies performed by public sources such as HTA bodies, i.e. NICE or Ontario HTA were very highly rated, above 85 scores (66, 70, 97, 98). Overall, we found that most of the studies were of good or fair quality except for two papers which scored below 50.

DISCUSSION

Altogether, 46 papers were included in this systematic review. We identified three systematic reviews previously conducted for targeted therapies in mCRC (110-112), although they are different from ours in terms of the interventions focused. We focused on predictive biomarkers (or, companion biomarkers) and thus, targeted therapies with no licensed companion diagnostics were not included.

Our review is more comprehensive than previous studies. We identified and screened a much higher number of papers ($n=2893$) and conducted longer periods of literature search (17.5 years between 2000 and June 2018). And finally, we included the highest number of studies in the review ($n=46$) despite the narrower focus on predictive biomarkers with targeted therapies, while excluding cost-effectiveness analyses of targeted therapies with no licenced companion biomarkers.

Lange et al. (113) which focused on assessing the cost-effectiveness of monoclonal antibodies rather than that of biomarkers, is not directly comparable to our review. However, they provisionally suggested that KRAS testing is cost-effective compared to no-

testing. They found that treatment with bevacizumab, cetuximab, and panitumumab was generally not cost-effective. They assessed the quality of identified papers but did not synthesize the results even qualitatively. Frank and Mittendorf (114) focused on pharmacogenomic profiling prior to the administration of pharmaceuticals in mCRC. They observed that the application of predictive biomarkers prior to EGFR antibodies was cost-effective but the cost-effectiveness of biomarkers for irinotecan-based chemotherapy remained unclear. They provided qualitative synthesis on key drivers and areas of uncertainty in the included studies. First, they found that biomarker costs were a driver of cost-effectiveness. Second, the characteristics of biomarkers such as performance accuracy and time of testing influence cost-effectiveness. Third, limited availability of clinical data is a source of uncertainty, especially because the efficacy of biomarkers is determined by the effects of subsequent therapies. Both reviews (113, 114) suggested that the addition of KRAS testing prior to treatment could be more cost-effective than a no-testing strategy. The most recent systematic literature review was done by Guglielmo et al (112), focusing on genetic tests of Lynch syndrome (LS) and KRAS mutation tests. But their search covers a very short period and search strategies were not performed step by step. Overall, none of the studies synthesized the cost-effectiveness results of predictive biomarkers for corresponding therapies even qualitatively, although they assessed the quality of identified studies. To the best of our knowledge, this is the first paper that analysed the cost-effectiveness of predictive biomarkers and corresponding therapies separately and analysed the interactions between them in terms of the influence of predictive biomarkers on the cost-effectiveness of subsequent therapies.

We found that most studies used a third-party payer perspective such as health care systems or national health insurances, often taking account of only direct costs in their evaluations. Three studies included both direct and indirect costs from a societal

perspective (72, 105, 107). Zhou et al. (72) stated that they evaluated from a perspective of Chinese health care system, however, we categorised their study as having a societal perspective since they considered indirect costs as well i.e., travel fees and absenteeism fees. Although a general view is that it is appropriate to include both direct and indirect costs in cost-effectiveness analyses (3), it is not commonly practised in performing economic evaluations for pharmaceutical products especially when aimed to get reimbursed. Consequently, few economic evaluations have taken a societal perspective (n=3) as seen in Appendix 2-3 **Error! Reference source not found.** Without the changes to the HTA guidelines for reimbursement in respective countries, this trend won't be reversed. For example, Krol et al. (107) conducted their study from two perspectives, a HCS perspective for Belgium and societal perspective for Netherlands, following the respective country's HTA guidelines.

When conducting a comparative analysis such as cost-effectiveness analyses, it is methodologically and ethically important to use the most appropriate alternative therapy as a comparator strategy. Standard of care (SOC) is the most widely accepted comparator in economic evaluations according to cost-effectiveness analysis guidelines in many countries. However, we found that a majority of economic evaluations of biomarker-guided therapies were performed in a pre-defined genetic group (n=23) and by doing so, most studies failed to explicitly consider the values of predictive biomarkers in their comparative analyses.

Our finding that whether the use of biomarkers makes corresponding therapies more cost-effective is largely driven by the expected impact on health outcomes rather than on costs contrasts with that of Frank and Mittendorf (114). This finding also highlights that the cost-effectiveness analyses of targeted therapies should consider the sensitivity and specificity

of biomarker testing. Our review showed that only six studies included the clinical characteristics of the biomarker such as performance accuracy (30, 65, 70, 73, 74, 80). A considerable number of studies did not include this in their evaluations. For example, low sensitivity may lead to not giving targeted therapies to KRAS WT patients, whereas low specificity may lead to treating patients unresponsive to the therapy. Then, some of these patients may experience poorer outcomes owing to adverse events, compared to the comparator strategy of receiving BSC. Or, false negative test results may lead to not treating the responsive patients, which causes an accumulated loss of health benefits compared to the strategy of having all patients treated with the intervention without biomarker testing. Biomarker prevalence (proportion of patients with a biomarker status) was often not considered in evaluations.

Some limitations need to be acknowledged with regard to the present review. Systematic reviews are transparent, rigorous and reproducible and thus, are widely used to identify existing literature in many fields including health economics. However, literature searches using an electronic database may be limited by the performance of database filtering algorithms and indexers. Therefore, our review was supplemented by hand-searches using snowballing methods and references from other reviews as well as conference abstracts. Our review relies on published evidence in the public domain and consequently is vulnerable to publication bias. Given that quantitative synthesis of the study results of economic evaluations is not possible owing to heterogeneity across different countries and clinical settings, we performed the data synthesis qualitatively in order to provide a comprehensive view on the cost-effectiveness of predictive biomarkers for targeted therapies. As a typical example, economic evaluations of low-income countries such as Chinese studies are not comparable to that of high-income countries in terms of willingness to pay thresholds and healthcare systems.

In conclusion, companion biomarkers for targeted therapies in mCRC were mostly found to be cost-effective; otherwise, they improved the cost-effectiveness of corresponding therapies by saving some costs. However, they did not necessarily make the corresponding targeted therapies cost-effective. Biomarker's clinical and economic inputs captured in economic evaluations of targeted therapies were often limited to the cost of tests and these values were frequently omitted especially when the scope of comparative analysis was limited to a pre-defined genetic population. In addition, we observed that there is no consensus on the best practice of strategy comparisons and no consistency in how to compare alternative strategies to estimate the ICERs of cancer biomarkers for targeted therapies in mCRC.

3. HOW ARE WE ASSESSING THE VALUE FOR MONEY OF CANCER BIOMARKERS IN ECONOMIC EVALUATIONS?

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	299429	Title	
First Name(s)	Mi Kyung (Kelly)		
Surname/Family Name	Seo		
Thesis Title	Economic evaluations of cancer biomarkers for targeted therapies		
Primary Supervisor	John Cairns		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

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SECTION C – Prepared for publication, but not yet published


Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Not yet submitted

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	
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SECTION E

Student Signature	
Date	

Supervisor Signature	
Date	29 November 2019

3.1. Research paper II

Title: How are we assessing the value for money of cancer biomarkers in economic evaluations?

Author: Mikyung Kelly Seo^{1,2}, John Cairns^{1,2}

Affiliations: ¹ Department of Health Services Research and Policy, Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom. ² Centre for Cancer Biomarkers (CCBIO), University of Bergen, Bergen, Norway.

Publication status: Not yet submitted.

Contribution of the candidate to this paper: As the first author, I conceptualised and designed the study. I developed the literature search and review protocol using the PICOS framework including the literature search strategy for each electronic database searched. I conducted the literature search including hand searches. I then performed the two-stage screening of all literature (the 1st screening of title and abstract of literature; the 2nd screening of full-text literature). I developed the data extraction form to maintain consistency in extracting data across all the papers included in the review. I investigated and processed the extracted data for formal analysis and data synthesis. I wrote and produced the entire manuscript. It was then reviewed by my PhD supervisor, John Cairns.

ABSTRACT

Background

Despite the increasing economic assessment of companion biomarkers, no agreement exists whether existing methods are sufficient or whether different methods might produce different cost-effectiveness results.

Objectives

This study reviews economic evaluations of companion biomarkers for targeted therapies and synthesizes the current practices and issues. It highlights the challenges to be overcome to reach a consensus on methods and data requirements for economic evaluations of cancer biomarkers.

Methods

A literature search was performed using Medline, Embase, EconLit, Cochrane library. Articles published from 2014 to 2018 were searched. Economic evaluations on biomarker-guided therapies with companion diagnostics in cancer were searched. To make studies more comparable, data extraction and analysis was performed based on ten key areas of methods where consensus is lacking when modeling companion biomarkers in the assessments of co-dependent targeted therapies.

Results

Eighteen papers were included in this review. All studies modelled the costs of companion biomarker testing in economic evaluations. Three out of eighteen studies found to be of good quality in incorporating model inputs relevant to companion biomarkers in economic evaluations. The most frequently ignored areas were preference-based outcome, clinical

utility, resource use, and the timing of the test. No consistent approaches were found to be existent in the current practices of assessing and reflecting the value of companion biomarkers as part of the economic assessment of targeted therapies in oncology.

Conclusion

Although no consistency exists in the current practices of evaluating companion biomarkers, some common patterns found to be useful to provide possible solutions in evaluating and capturing the full value of companion biomarkers beyond sensitivity/specificity and cost related to biomarker testing.

INTRODUCTION

Economic evaluations (EEs) are increasingly used to inform market access, reimbursement and coverage of new medical technologies including biomarker diagnostics for targeted therapies. Companion biomarkers are used to select and guide the best treatment options for patients prior to the administration of a corresponding therapy. However, no agreement exists whether existing methods are sufficient to evaluate the health economic impact of biomarkers, or whether different methodological approaches might produce conflicting results with regard to the cost-effectiveness of biomarkers or biomarker-guided therapies.

This study focuses on companion biomarkers for targeted cancer therapies. Specific biomarkers, known as companion diagnostics (CDx) are the focus of this review. CDx can be defined as a medical device (often *in vitro*) providing information for the safe and effective use of a corresponding intervention (1). CDx is the diagnostic test labelled to be used prior to the administration of a particular therapeutic product and thus, the

treatment decision is made based on the biomarker testing result. That is, the use of a specific test is obligatorily proceeded by the provision of corresponding therapy (e.g. HER2 testing prior to trastuzumab). If test accuracy is not satisfactory, the treatment decision may detrimental to the patient outcomes when treated with the biomarker-guided therapy.

This study reviews current methodological approaches and challenges in EEs of cancer biomarkers. It highlights the complexity of evidence generation faced by test developers without clear guidance on evidentiary standards and data requirements. It aims to analyze the approaches currently adopted in EEs of biomarkers and to identify current practices and address policy implications. This review focuses on biomarkers co-licensed with therapeutic products, namely CDx. Also, the methodological issues commonly relevant to the classical therapeutic interventions are not of interest in this review. It only considers methodological challenges and issues faced in the evaluation of biomarker tests which do not arise with the evaluation of pharmaceutical drugs.

METHODS

A systematic review of model-based health economic evaluations of companion diagnostics for targeted cancer therapies was undertaken. This review was conducted followed by recommendations of the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines (116, 117).

Literature search

A systematic literature search was conducted for EEs of cancer biomarkers co-licensed for the use of targeted therapies (hereafter, called “companion biomarkers”). Medline (Ovid),

Embase (Ovid), EconLit, Cochrane library were used. Hand search was done by reviewing article citations and review articles. Four articles were then identified(68, 118-120).

The electronic search was performed using Medical subject heading (MeSH) terms and keywords that were developed for disease (cancer), intervention (companion biomarkers for targeted therapies), and study design (economic evaluations). These were combined with free-word texts using relevant economic terms (e.g. “cost-effectiveness”) and the names of biomarker-guided therapeutic products both in brand and generic terms. The list of CDx approved by the US Food and Drug Administration (FDA) (37) was targeted in the literature search. Studies published in English were searched from 2014 to 2018. The 5-year search period was chosen given that this literature review aimed to explore current EE practice and to critically appraise them in depth. Five years was considered to be long enough to capture a sufficient number of recently published EEs and also to exclude any out-of-date approaches not applicable to current practice. Search terms are provided in Appendix 3- 1 .

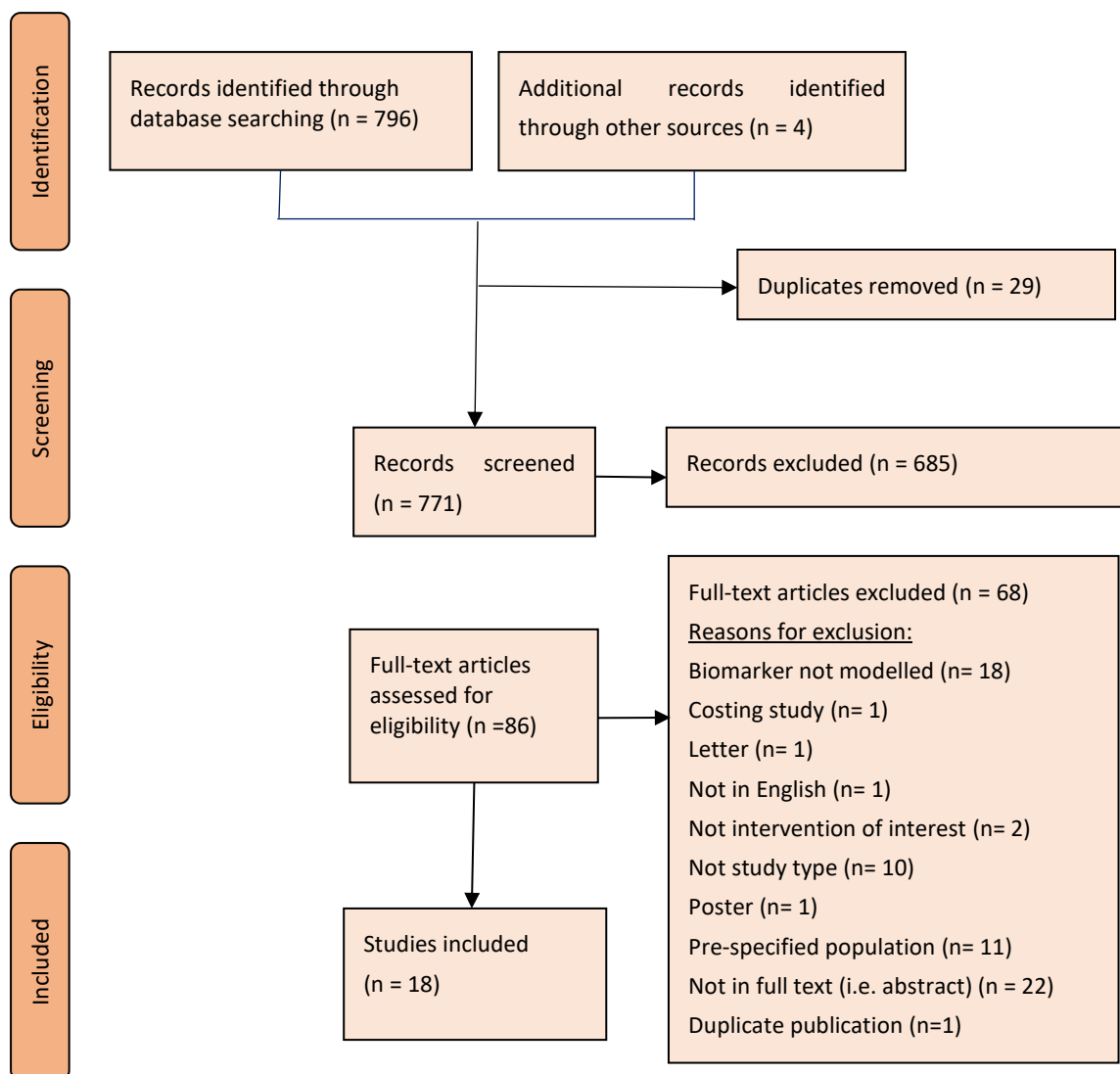
Study selection

Studies were selected using pre-specified inclusion and exclusion criteria based on the PICOS framework. Details are provided in Appendix 3- 2 . Given the aims of this literature review, studies failing to report important information relevant to EEs of a companion biomarker (e.g. biomarker characteristics, biomarker-related modeling inputs) were excluded.

The study selection had three stages. First, identified articles from electronic databases were imported into EndNote® and duplicate citations removed. Second, the title and

abstracts of the identified articles were screened to assess suitability by the first reviewer (MKS) and the studies clearly indicated as irrelevant were excluded but any studies with ambiguity were discussed with the second reviewer (JC). Third, remaining articles that met the inclusion criteria were read in full text by the first reviewer (MKS) and cross-checked by the second reviewer (JC). Any disagreements in all stages were resolved by discussion between two reviewers (MKS, JC) (Figure 3-1Error! Reference source not found.).

FIGURE 3-1 : PRISMA FLOW DIAGRAM OF STUDY SELECTION



Data analysis and synthesis

Ten methodological areas were selected to focus on in reviewing the current practices of methodological approaches of EEs for companion biomarkers. These key areas were formulated based on previous studies (51, 121-123), and partly on the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (124) and from our experience working in health technology assessments of cancer biomarkers for targeted therapies. The ten areas are as follows: (i) target population; (ii) viewpoint of analysis; (iii) the choice of alternative strategy arm(s); (iv) structure of comparative analysis (or structure of strategy comparisons); (v) measurement of clinical value of companion biomarkers; (vi) measurement and valuation of preference-based outcomes of companion biomarker tests; (vii) estimating resource use and costs; (viii) timing of the test use; (ix) uncertainty analysis; (x) data sources for biomarker-related data inputs. The narrative syntheses and analyses were performed for these ten methodological areas. To be more specific, a list of questions was developed based on these items (**Error! Reference source not found.**).

TABLE 3-1 : A LIST OF KEY METHODOLOGICAL ITEMS IN REVIEWING THE EEs OF BIOMARKER-GUIDED THERAPIES

Question items	Yes	No
Q1. Did the EE target all patient groups regardless of biomarker status of test positive, negative, unknown?		
Q2. Did the EE justify the viewpoint of analysis? (I.e. Analysis perspective; third-party payer, society, hospital, etc.)		
Q3. Was the standard of care chosen as a comparator strategy?		
Q4. Was the test-treat strategy compared to the comparator strategy arm(s)?		
Q5. Was the clinical effectiveness of the companion biomarker test considered in the economic models? If not considered, justification/assumption provided?		
Q6. Were preference-based outcomes of companion biomarker tests were considered in the economic models? If not considered, has the assumption been provided with justifications?		
Q7-1. Were the details of the resource consequences of the use of companion biomarker testing considered and reported?		

Q7-2. Were the costs of companion biomarker test(s) considered and reported?		
Q8. Different timing of the test(s) was considered and reported? (i.e. at the time of diagnosis, at the time point of progression to metastasis, etc.)		
Q9. Was uncertainty with respect to the characteristics of the companion biomarker test(s) explored? (i.e. at least one component of the characteristics of biomarker test was tested; such as cost, cut-off threshold, sensitivity/specificity)		
Q10. Were the data sources for the model inputs clearly reported and justified? (i.e. meta-analysis, clinical trials, published papers, etc.)		
Q11. Was the name/type of biomarker test specified? (e.g. Cobas® BRAF V600 mutation test)		
Q12. Was the frequency/prevalence of biomarker status considered in the economic model? If not, has this been justified?		

RESULTS

Overall, eleven papers assessed the cost-effectiveness of the corresponding drugs (87, 102, 125-134), while seven papers evaluated the cost-effectiveness of companion biomarkers per se (68, 69, 72, 118, 135-137). The most frequently used modeling type was a Markov model (eleven papers), followed by partitioned survival model (two papers) and semi-Markov model (two papers). All economic evaluations were performed from a third-party payer perspective except for one study which took a societal perspective. All studies were performed for high income countries except for four studies of China.

The overview of the included studies analyzed by the list of questions is provided in Appendix 3-3. Study characteristics are synthesised by key items in Figure 3-2 and detailed in Table 3-2. The most frequently ignored model inputs related to companion biomarkers were preference-based outcomes, clinical utility, resource use, and the timing of the test.

Figure 3-2 : Graph of including the characteristics of companion biomarkers in economic evaluations

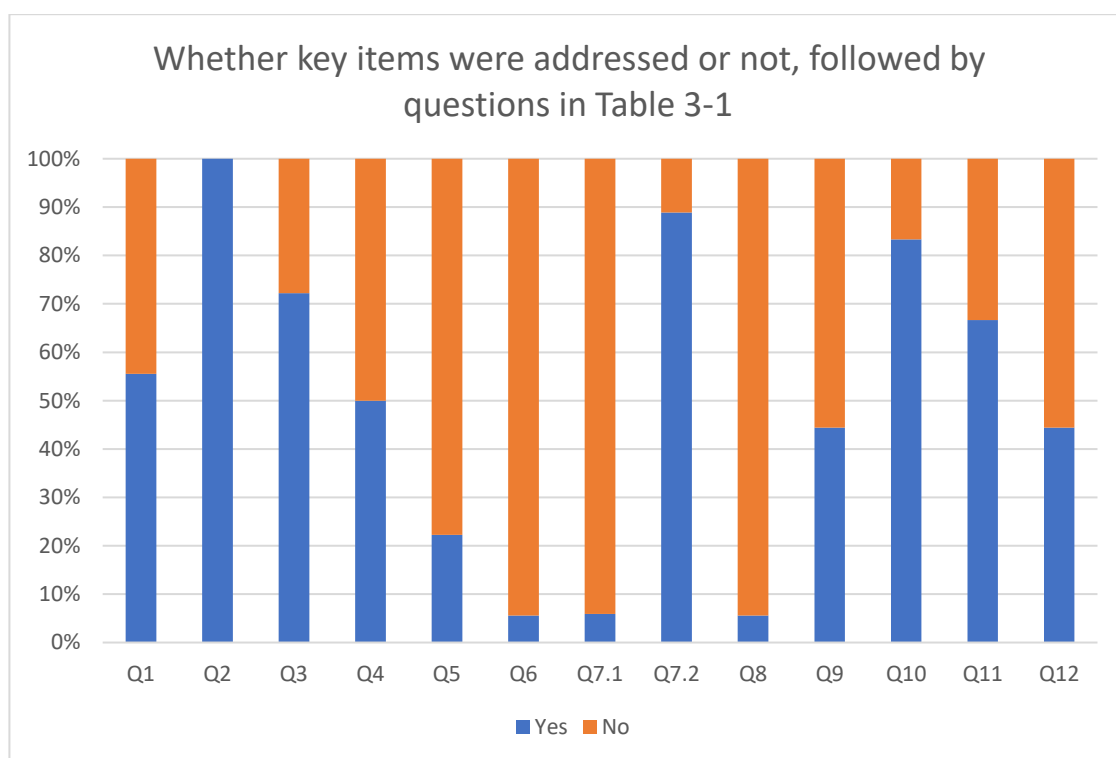


TABLE 3-2 : DETAILED CHARACTERISTICS OF THE INCLUDED STUDIES

Study	Focu -s	Objective	Biomarker test	Corresponding therapy compared	Strategies compared	Biomarker related model inputs considered	Country	Perspecti -ve	Model type	Time horizon	Outcome measure	Funding
Aguiar 2017	Rx	To assess cost-effectiveness of immune checkpoint inhibitor with and without the use of PD-L1 testing for patient selection.	PD-L1 expression.	Immunotherapy (Nivolumab, Pembrolizumab, Atezolizumab)	3 strategies compared: Treat-all with docetaxel. Treat-all with immunotherapy. Test-treat (if PD-L1 expressed with 1% or more, patients were treated with immunotherapy; if not, treated with docetaxel.)	PD-L1 testing cost. PD-L1 expression cut-off points (PD-L1>1% used in base-case analysis, while 5%, 10%and 50% tested in sensitivity analysis.)	USA	Third-party payer.	Decision - analytic model. (No further details given.)	5-year horizon	QALY	No funding declared.
Chouaid 2017	Rx	To assess the cost-effectiveness of afatinib versus gefitinib for EGFR mutation-positive NSCLCs.	EGFR mutation.	Afatinib, Gefitinib.	2 strategies compared on pre-specified patients: Treated with afatinib. Treated with gefitinib.	EGFR testing cost.	France	Third-party payer.	Partitioned survival model.	10-year horizon.	QALY	Commercial funding.
Curl 2014	Rx	To compare three strategies (dacarbazine, vemurafenib, vemurafenib plus ipilimumab) for patients with BRAF positive metastatic melanoma.	BRAF mutation.	Dacarbazine, Vemurafenib, Vemurafenib plus Ipilimumab	3 strategies compared on pre-specified patients: Treated with dacarbazine. Treated with vemurafenib. Treated with vemurafenib plus ipilimumab.	BRAF testing cost (Cobas®)	USA	Third-party payer.	Decision tree model.	Lifetime	QALY	No funding.

Ewara 2014	Rx	To assess the cost-effectiveness of three strategies (bevacizumab plus FOLFIRI, cetuximab plus FOLFIRI, panitumumab plus FOLFIRI) for mCRC patients with KRAS WT.	KRAS mutation.	Bevacizumab, Cetuximab, Panitumumab.	3 strategies compared on pre-specified patients: Treated with bevacizumab plus FOLFIRI. Treated with cetuximab plus FOLFIRI. Treated with panitumumab plus FOLFIRI.	KRAS testing cost.	Canada	Third-party payer.	Markov model	100-month horizon.	QALY	No funding.
Graham 2014	Rx	To assess the cost-effectiveness of panitumumab plus mFOLFOX6 compared with bevacizumab plus mFOLFOX6.	RAS mutation.	Panitumumab, Bevacizumab.	2 strategies compared on pre-specified patients: Treated with panitumumab plus mFOLFOX6. Treated with bevacizumab plus mFOLFOX6.	KRAS and RAS testing cost. RAS frequency.	USA	Third-party payer.	Semi-Markov model.	Lifetime	QALY	Commercial funding.
Graham 2016	Rx	To assess the cost-effectiveness of subsequent-line treatment with cetuximab or panitumumab in patients with WT KRAS mCRC.	KRAS mutation.	Cetuximab, Panitumumab.	2 strategies compared on pre-specified patients: Treated with cetuximab. Treated with panitumumab.	KRAS testing cost.	USA	Third-party payer.	Semi-Markov model.	Lifetime	QALY	Commercial funding.
Harty 2018	Rx	To investigate the clinical effectiveness and cost-effectiveness of panitumumab plus chemotherapy and cetuximab plus chemotherapy for rat sarcoma (RAS) wild-type (WT) patients for the	KRAS/RAS mutation.	Cetuximab.	2 strategies compared: Treated with FOLFIRI alone. Treated with cetuximab plus FOLFIRI.	EGFR testing cost. RAS testing cost.	UK	Third-party payer.	Markov model.	10-year horizon.	QALY	Commercial funding.

		first-line treatment of mCRC.										
Huxley 2017	Rx	To investigate the clinical effectiveness and cost-effectiveness of panitumumab plus chemotherapy and cetuximab plus chemotherapy for RAS wild-type (WT) patients for the first-line treatment of mCRC.	RAS mutation.	Cetuximab, Panitumumab.	5 strategies compared on pre-specified patients: Treated with FOLFOX/FOLFIRI. Treated with cetuximab plus FOLFOX/FOLFIRI. Treated with panitumumab plus FOLFOX.	RAS testing cost. RAS prevalence (50% of patients assumed to be RAS wild-type).	UK	Third-party payer.	Markov model.	30-year horizon.	QALY	Governmental funding.
Janmaat 2016	Rx	To determine the ICER of adding cetuximab to first-line chemotherapeutic treatment of patients with advanced esophageal squamous cell carcinoma (ESCC), based on RCT II trial.	EGFR expression.	Cetuximab.	2 strategies compared on pre-specified patients: Treated with cetuximab plus cisplatin-5-fluorouracil. Treated with cisplatin-5-fluorouracil.	EGFR testing cost. EGFR prevalence (60% patients assumed to be EGFR positive).	Netherlands	Third-party payer.	Monte Carlo simulation using individual patient data.	0.9 years.	QALY	No funding.
Lim 2016	Dx	To evaluate the cost-effectiveness of treating patients guided by EGFR testing compared to no-testing (which is current practice in South Korea).	EGFR expression.	Erlotinib.	2 strategies compared: Test-treat (if EGFR positive, treated with erlotinib; if EGFR wild-type, treated with conventional chemotherapy; if unknown, re-biopsy required). No-testing (Treat all with conventional chemotherapy).	EGFR testing cost (Therascreen®, Cobas®). Testing accuracy (sensitivity/specificity).	South Korea.	Third-party payer.	Markov model.	5-year horizon.	QALY	Governmental funding.

Lu 2018	Dx	To examine the economic outcome of three techniques for testing ALK gene rearrangement combining with crizotinib (first-line), compared with traditional regimen.	ALK gene rearrangement	Crizotinib.	3 ALK rearrangement testing techniques prior to crizotinib were compared (4 strategies compared): No gene screening - all treated with standard chemotherapy. Ventana IHC - if ALK rearrangement positive, treated with crizotinib; if ALK rearrangement negative, treated with standard chemotherapy. qRT-PCR - if ALK rearrangement positive, treated with crizotinib; if ALK rearrangement negative, treated with standard chemotherapy Conventional IHC - if IHC ALK rearrangement negative, treated with standard chemotherapy; if IHC ALK rearrangement positive, FISH testing (to confirm) to be performed and then, if FISH ALK rearrangement negative, treated with standard chemotherapy, if FISH ALK rearrangement positive, treated with crizotinib.	Cost of ALK rearrangement testing (Ventana IHC; IHC; qRT-PCR; FISH) Sensitivity and specificity respectively for Ventana IHC; IHC; qRT-PCR). ALK prevalence	China	Third-party payer.	Markov model.	10-year horizon.	QALY	Commercial funding.
Morgan 2017	Rx	To assess the cost-effectiveness of crizotinib in untreated anaplastic lymphoma kinase-positive (ALK-positive) non-small-cell-lung cancer (NSCLC).	ALK expression.	Crizotinib	2 strategies compared on pre-specified patients: Treat all with crizotinib. Treat all with pemetrexed chemotherapy in combination with cisplatin or carboplatin.	ALK testing cost ImmunoHistoChemistry (IHC) testing cost Fluorescence in situ hybridisation (FISH) testing cost	UK	Third-party payer.	'area-under-the curve' Markov model.	15-year horizon	QALY	Governmental funding.
Wen 2015	Dx	To explore the costs and effectiveness of RAS screening before	RAS mutation.	Cetuximab, Bevacizumab.	Four strategies compared:	KRAS/RAS testing cost.	China	Third-party payer.	Markov model.	10-year horizon.	QALY	No funding.

		monoclonal antibodies in mCRC based on FIRE-3 study.			<p>KRAS tested - treated with cetuximab and FOLFIRI.</p> <p>RAS tested - treated with cetuximab and FOLFIRI.</p> <p>KRAS tested - treated with bevacizumab and FOLFIRI.</p> <p>RAS tested - treated with bevacizumab and FOLFIRI.</p>							
Westwood 2014	Dx	To compare the performance and cost-effectiveness of KRAS mutation tests in differentiating adults with mCRC who may benefit from first-line treatment of cetuximab in combination with standard chemotherapy from those who should receive standard chemotherapy alone.	KRAS mutation.	Cetuximab.	<p>10 different tests for KRAS mutation status. No comparator approach taken.</p> <p>Cobas KRAS Mutation Test Kit (Roche Molecular Systems).</p> <p>Therascreen KRAS RGQ PCR Kit (QIAGEN).</p> <p>Therascreen KRAS Pyro Kit (QIAGEN).</p> <p>KRAS LightMix Kit (TIB MOLBIOL).</p> <p>KRAS StripAssay (ViennaLab).</p> <p>HRM analysis.</p> <p>Pyrosequencing.</p> <p>MALDI-TOF mass spectrometry.</p> <p>Next-generation sequencing.</p> <p>Sanger sequencing.</p>	<p>KRAS testing cost.</p> <p>KRAS testing accuracy (sensitivity/specificity)</p> <p>KRAS prevalence (KRAS mutant, KRAS wild-type, KRAS unknown test result).</p> <p>Timing of the test – justifications given.</p>	UK	Third-party payer.	Markov model	Lifetime (23 years)	QALY	Governmental funding.
Wu 2017	Rx	To evaluate the economic outcome of adding cetuximab to the standard chemotherapy.	RAS mutation.	Cetuximab.	<p>2 strategies compared:</p> <p>No testing – treat all with FOLFIRI.</p> <p>Test-treat (if RAS wild-type, treated with cetuximab plus FOLFIRI, if RAS mutant, treated with FOLFIRI).</p>	<p>RAS testing cost.</p> <p>RAS prevalence.</p>	China	Third-party payer.	Markov model.	Lifetime	QALY	No funding.

Zhou 2016	Dx	To evaluate the cost-effectiveness of predictive testing for extended RAS WT status in the context of targeting the use of cetuximab/bevacizumab.	RAS mutation.	Cetuximab, Bevacizumab.	4 strategies compared: KRAS WT tested-treated with cetuximab plus chemotherapy. KRAS WT tested-treated with bevacizumab plus chemotherapy. RAS WT tested-treated with cetuximab plus chemotherapy. RAS WT tested-treated with bevacizumab plus chemotherapy.	KRAS/RAS testing cost.	China	Societal perspective.	Markov model.	Lifetime	QALY	No funding.
Saito 2017	Dx	To determine the cost-effectiveness of comprehensive molecular profiling before initiating anti-EGFR therapies in mCRC.	RAS mutation. Comprehensive profiling that includes PTEN + ERBB2, PTEN + SRC, and BRAF + RNF43 mutations (CancerPlex®).	Bevacizumab, Panitumumab.	3 strategies compared: No testing RAS screening Comprehensive screening	Biomarker testing cost. Proportion of molecular subgroups (proportion of patients per biomarker status).	Japan	Third-party payer.	Markov model	5-year horizon.	QALY	Unclear (Not reported)
Butzke 2015	Dx	To evaluate the cost-effectiveness of UGT1A1 genotyping in patients with mCRC undergoing irinotecan-based chemotherapy compared to no-testing.	UGT1A1 genotyping	Irinotecan	3 strategies compared: No testing-treat all with standard dose of irinotecan. Test-treat (if tested wild-type, standard dose of irinotecan treated; if hetero-and homozygotes, treated with a dose reduction of irinotecan by 25%). Test-treat (all patients receive standard dose, and hetero-and homozygotes additionally received the growth factor 'pegfilgrastim').	Sensitivity/specificity.	Germany	Third-party payer.	Markov model	Lifetime	QALY	No funding.

Rx; Drugs, Dx; Companion biomarker

Target population

The patient population targeted in EEs of biomarker-guided therapies was varied but it can be broadly classified into two categories; one is a subgroup of patients with a specific biomarker status confirmed and the other is a group of patients with disease conditions regardless of biomarker status. Eight studies were performed on a pre-defined group of patients with a particular biomarker status (87, 102, 126-128, 130-132) however, they considered at least one characteristic of companion biomarkers in their evaluations. Many EEs were conducted using a pre-specified patient group with a particular confirmed biomarker status, and authors used this to justify excluding some of the key characteristics of companion biomarkers from their evaluations. In addition, two studies were conducted on all patients regardless of biomarker status, while additional analyses were done for a subgroup of patients with a specific biomarker status (68, 129).

Analysis viewpoint

The analysis viewpoint defines the scope of costs and health benefits to be assessed in EEs; often referred to as study perspective. All included studies clearly reported the perspective of EEs conducted. A majority of studies showed that EEs were performed applying the third-party payer perspective. Only two studies stated that they employed a societal perspective (72, 127); one from China and the other from the US. However, the US study (127) was found to be more appropriately described as a third-party payer perspective (e.g. Medicare).

Given the nature of multiple purposes of biomarker testing application or use, and the indirect impact of companion biomarker diagnostics on patient health benefits, taking a

perspective of third party payers might not be sufficient to capture all costs and benefits relevant to companion biomarkers in the clinical context of selecting patients suitable for the corresponding therapy. However, only one study considered indirect costs such as travel fees and absenteeism costs together with the cost of adverse events (72). However, this study did not consider any biomarker-related indirect costs either. For example, Schnell-Inderst and colleagues conducted a targeted review and highlighted measuring the potential effect modifiers such as the dependency of treatment effects on contextual factors and learning curve (138).

Choice of treatment alternatives (comparators)

It is widely accepted that the alternative strategy to be compared in EEs should be based on the current practice with respect to the target population (139, 140). Several different types of comparator strategies were employed in the EEs of companion biomarkers for targeted therapies. These different strategies can be categorized in five forms as below. Some papers used more than one comparator strategy arm (102, 125, 136).

First, all patients were tested prior to the administration of the corresponding biomarker-guided therapy and treated depending on the test result. For example, if the patients tested positive for a particular biomarker, they received the guided therapy; however, they were treated with the non-guided therapy if they tested negative. This '*test-treat strategy*' strategy was often employed as an intervention strategy rather than as a comparator in EEs of companion biomarker therapies. Five studies employed this strategy type as a comparator (68, 69, 72, 136, 137) however, these studies focused on comparing the analysis among different biomarker types or testing kits rather than comparing biomarker-guided against non-guided strategy.

Second, patients were not tested but were treated with the biomarker-guided therapy; so-called '*no-testing-treat-all with the guided therapy*'. Only one study fell into this category (125). This study aimed to assess the cost-effectiveness of a new guided-therapy with and without the use of biomarker testing.

Third, no patients were tested but all patients were treated with the non-guided therapy; so-called '*no-testing treat-all with the non-guided therapy*'. Six studies used this strategy as their comparator (118, 125, 129, 133, 135, 136), and mostly a standard chemotherapy was chosen as the non-guided therapy.

Fourth, all patients modelled in EEs were already pre-specified like biomarker positive or negative, and all treated with the guided therapy; called '*biomarker-specified group treating all with the guided therapy*'. This type of comparator strategy is also commonly observed in EEs of biomarker-guided therapies in addition to the test-treat strategy. Two studies used this as their comparator strategy (102, 126). Both studies focused on assessing different guided therapies for the group of patients confirmed with a particular biomarker status. Only a handful of model parameters of companion biomarker tests were considered in their EEs and thus, they often failed to provide a full spectrum of decision-making information relevant to the use of companion biomarker medicines.

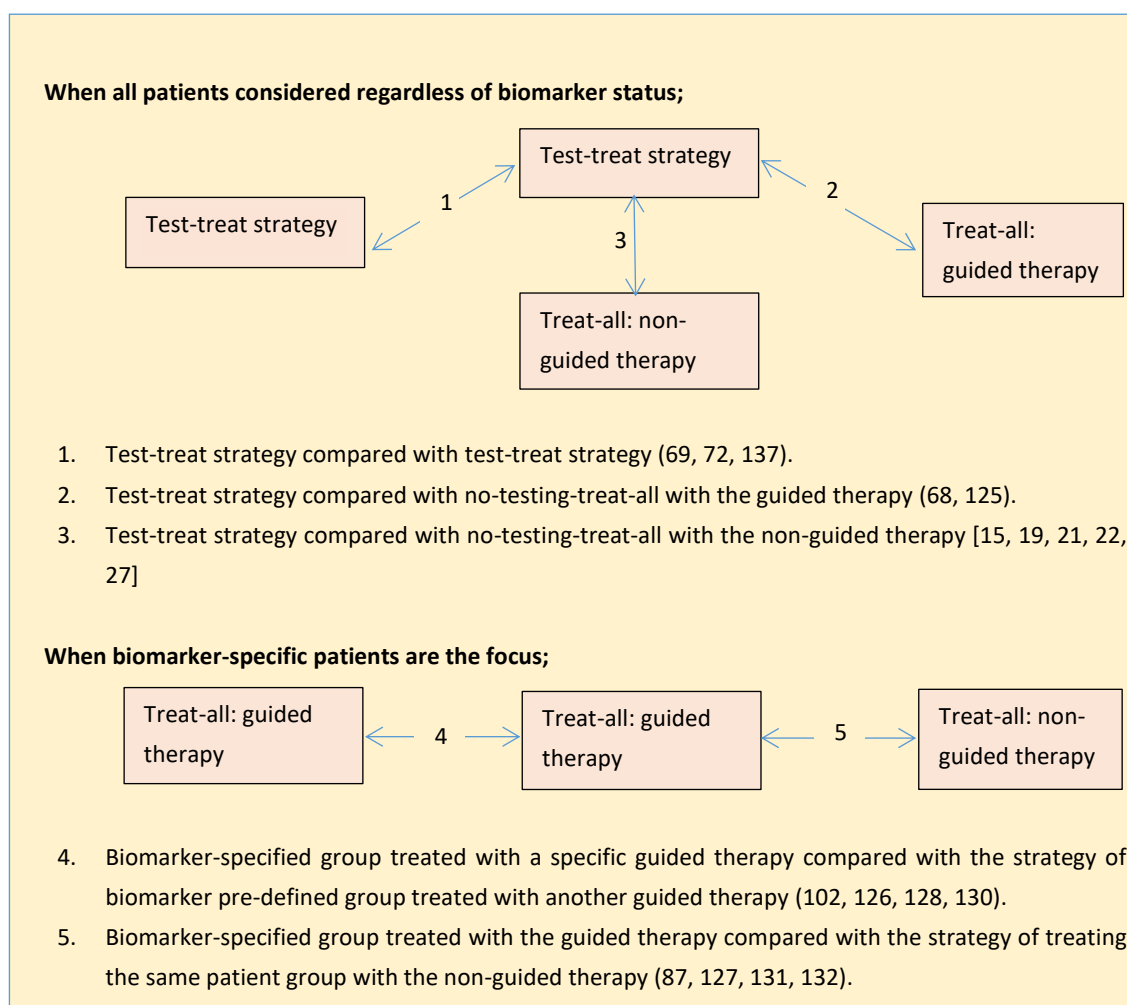
Fifth, all patients were biomarker positive or negative and treated with the non-guided therapy; called '*biomarker-specified group treating all with the non-guided therapy*'. Seven studies employed this as their comparator strategy (87, 102, 127, 128, 130-132). This strategy is the most frequently employed comparator arm in EEs of companion biomarker medicines in cancer.

Structure of strategy comparisons

We found a wide range of inconsistencies in structuring the strategies to be compared in EEs of companion biomarker therapies. Structuring the comparative strategy arms can be determined by various factors such as eligible patient populations, decision-making bodies' EE guidelines, and local clinical settings. For example, an EE study aiming to compare a guided therapy against a standard of care applied the structure of comparing the test-treat therapy against treat-all with the guided therapy or with the non-guided therapy. Or, a similar study aiming to assess the cost-effectiveness of a new therapy with or without biomarker testing could employ the comparative structure of a testing strategy against a no-testing strategy on a particular group of patients with known biomarker status. The structure of comparing strategies in comparative analysis can be classified into five types as described in Figure 3-3.

The comparative structure of applying strategy arms in EEs of companion biomarkers was so varied, it would likely lead to a different or even conflicting conclusion in terms of cost-effectiveness of companion biomarker therapies depending on the comparator strategy chosen.

FIGURE 3-3 : STRUCTURE OF COMPARING STRATEGIES IN EEs OF COMPANION BIOMARKER THERAPIES



Measuring the clinical value of companion biomarkers

No consensus currently exists on data requirements when incorporating the clinical value of biomarkers into the modeling of EEs of biomarker-guided therapies. For example, the Diagnostic Assessment Program requires testing accuracy in appraisal of diagnostic tests (25), although it is not always feasible in practice especially when assessors are faced with no data on test accuracy at all . On the other hand, NICE methods guide of technology appraisal does not necessarily require the testing accuracy but requires the incorporation of the associated costs of biomarker testing (139). Furthermore, none of the EEs reviewed examined the accuracy of a companion biomarker diagnostic test separately, for example

by testing different cut-off thresholds including false positive and false negative results as part of uncertainty analysis. The cut-off threshold is the cut-off point defining the presence of the biomarker, determining biomarker-positive and biomarker-negative patients for the administration of corresponding co-dependent therapeutic agents (141-143). Varying levels of accuracy may lead to different patient subgroups being eligible for the corresponding drugs. According to previous studies (51, 122), the clinical value of biomarker tests could be assessed in three ways; analytic validity, clinical validity, and clinical utility. Analytic validity is about how well a test detects the presence or absence of a particular marker (140). Clinical validity refers to the performance of a test (diagnostic accuracy) in detecting the presence of a specific disorder; so-called sensitivity and specificity (122). Clinical utility is defined in the ACCE (analytical validity, clinical validity, clinical utility, and ethical/legal/social implications) model project as “how likely the test is to significantly improve patient outcomes”, which goes beyond sensitivity and specificity and then which may change treatment options for the patient (144). In other words, clinical utility (effectiveness) of companion testing technology is based on the ability to improve patient health outcomes by altering treatment decisions (145, 146).

Relatively few EEs considered the diagnostic accuracy of biomarker testing using data on sensitivity and specificity (135-137). Many EEs did not consider the performance of biomarker testing or often did not mention this at all (68, 72, 87, 102, 118, 125-128, 131). Otherwise, some studies provided some assumptions or justifications why they did not consider the clinical value of a companion diagnostic test (69, 129, 130, 132, 133). It is often assumed that the technical accuracy of patient stratification by biomarker testing is perfect and thus, the sensitivity and specificity were either not considered or assumed to be 100%. However, no studies explicitly considered or assumed the clinical utility of companion biomarkers in their EEs. For example, no studies stated that the clinical value

of companion biomarker testing was supposedly incorporated into the clinical effectiveness of the corresponding drug based on the clinical trial of the sub-population delineated by the diagnostic.

Meanwhile, a handful of studies considered the frequency or prevalence of a particular biomarker status among their target patient populations (68, 87, 131, 135-137). Among them, only one study considered the probability of unknown test result in the analysis (137).

Measurement and valuation of preference-based outcomes

The quality-adjusted life-year (QALY) is a preference-based health outcomes widely used in EEs of therapeutic products(3, 24). It is widely accepted because it allows comparisons of health benefits and costs across different disease areas and therapeutic interventions. However, challenges emerge with the economic assessment of companion biomarkers given the nature of targeted therapies guided by companion biomarker testing and indirect impact of companion biomarker testing on patient outcomes. The current metrics for measuring preference-based outcomes using population-based preferences cannot fully capture patient preferences for biomarker tests (147). There seems to be more aspects of individual patient preference when valuing biomarker tests compared to the valuation of conventional drugs. For example, patients could be informed in advance of the likelihood of therapeutic response or unresponsiveness prior to the provision of treatment.

Or, patients can have an improved sense of controlling their own choices of therapeutic options informed by their biomarker status. Shared decision making (SDM) and communication between patients and clinicians will put patients at the centre of treatment

decisions guided by companion biomarker test results. Patients may feel empowered to make informed decisions about their own treatment and care (148-150). Although the provision of biomarker-guided therapy is dictated by the patient's biomarker status, being informed of the biomarker status can support the SDM of both clinicians and patients to explore more fully the potential benefits and risks. It can then potentially improve patient satisfaction with health services.

Or, companion diagnostics for cancer patients usually require collecting a bio-sample for analysis, and this gives rise to the existence of process utility (including reassurance or information) (151-153). Brennan and Dixon's study (154) supported the existence of process utility and found that different approaches were being used to detect and measure process utility such as gamble techniques, time trade-off, conjoint analysis. Some biomarker tests involve relatively invasive methods to collect the bio-sample, such as tissue biopsy, needle biopsy, skin biopsy in diagnosing cancer (155, 156), that can be measured and incorporated into QALY estimates. Yet, how to measure and incorporate process utility into cost-utility analyses needs to be further researched with more empirical studies in HTA. Or, if companion biomarker tests were already integrated into the clinical study of measuring patient reported outcomes (PROs) for co-dependent therapeutic agents, it can be assumed that the disutility or utility value of companion biomarker testing is already embedded or indirectly expressed in PROs of the corresponding therapy. Yet, this aspect should be transparently reported in health economic models of companion biomarkers or biomarker-guided therapies. Nevertheless, none of the EEs included in this systematic review discussed these aspects of companion biomarker testing or indicated how preference-based outcomes of companion biomarker devices were measured and valued. For example, no studies explicitly included utility or disutility values for biomarker testing. Where biomarker testing uses tissues collected in a previous biopsy, it can be

argued that patient preferences do not need to be considered in the economic modeling. However, none of the EEs mentioned this aspect or attempted to justify the omission of preference-based outcomes of biomarker testing. As an example, patients might need to undergo another biopsy for the purpose of biomarker testing after the cancer has progressed to metastasis. Or, a second biopsy might be needed to confirm the biomarker status when the testing accuracy was unsatisfactory. Or, turnaround time of biomarker testing may lead to additional waiting time for patients to access the treatment. Or, patients might experience anxiety or hopelessness when they are informed that the test predicts non-response to the targeted therapy and no alternative therapy options are available.

Estimating resource use and costs

All included EE studies considered the costs of biomarker testing however, some details were ignored. Some papers did not report the cost of biomarker testing devices (125) and often a total lump sum cost was modelled without providing details on how the total cost calculated (69, 72, 102, 126, 127, 131). Several studies reported at least some details regarding data source or the names/types of biomarker testing kits (68, 87, 118, 128-130, 132, 133, 135, 136), but many EEs did not consider or report the resource use parameters relevant to the testing of companion biomarkers. None of the studies considered the capital cost related to the initial purchase of a biomarker test kit or diagnostic equipment as well as other costs such as training staff, relevant consumables, or lab reporting tools. Even in the situation where laboratories can re-purpose existing testing platforms to deliver the new test, relevant costs of consumables and staff with appropriate skills need to be considered. As an example, the NICE committee was aware that ALK testing would

be not carried out in this specific clinical setting if crizotinib was not available (157), and therefore it is highly likely that the hospitals will need to purchase the testing equipment (i.e. capital costing items) however, it was not considered in their EE.

Timing of the test use

Details of where in the clinical pathway testing was undertaken were often not reported. Only two studies (68, 137) provided some explanation on this aspect, however, it was not clear how the timing of the test use was considered in the analysis of the Westwood study (158). Whereas, Saito and colleagues (68) provided and justified their assumptions. Given the nature of companion biomarkers, the health benefit to the patient arises from the corresponding therapy guided by the testing result, which is best understood as it being part of the clinical pathway in relation to its indirect impact on patient outcomes. Therefore, the value of companion biomarkers is best assessed while considering the timing of the test use; for example, whether the testing was done at diagnosis or following progression to metastasis. Westwood and colleagues (137) noted that the timing of KRAS testing may vary; some clinicians might undertake routine testing for all patients at diagnosis or some might wait until metastases have been detected. Yet, they did not specify how their evaluation was done in this respect.

Uncertainty analysis

Six studies (125, 129-131, 135, 136) explored the impact of cost-effectiveness of varying at least one component of the characteristics of companion biomarker tests being evaluated such as unit cost, total testing cost, test accuracy, cut-off thresholds, and biomarker

prevalence. However, many studies did not examine the characteristics of a test separately from that of the corresponding therapy. According to HTA guideline, “if a diagnostic test to establish the presence or absence of the biomarker is carried out solely to support the treatment decision... a sensitivity analysis should be provided without the cost of the diagnostic test” (139). However, out of three UK studies, two studies performed a sensitivity analysis on biomarker testing cost (129, 130).

Data sources for biomarker-related data inputs

All papers except for three studies (102, 125, 131) provided data sources used for the characteristics of biomarker tests. However, several studies did not provide a specific name of companion biomarker testing kits, although some of them reported a general biomarker testing type (e.g. RAS testing) and therefore, several studies were not transparent and reproducible. The most frequently used data sources were previous published literature. However, testing cost inputs were mostly sourced from reimbursement schedules (127-129, 131, 133), manufactures or laboratories (72, 87, 137), and if such information was unavailable, expert opinions were sought (130).

DISCUSSION

Altogether, eighteen papers were included in this review. One existing systematic review found to be similar to this study in terms of study scope and objective (121). However, it mainly focused on reviewing the sensitivity and specificity of companion diagnostics and the cost of testing. It did not provide a comprehensive review of methodological approaches to EEs for assessing the value for money of companion biomarkers in the

context of precision medicine. To the best of our knowledge, this is the first review providing a comprehensive report on current practices and possible solutions in terms of methodological approaches and evidence requirements in assessing the value for money of companion biomarkers. Table 3-3 summaries possible solutions and suggestions to address the methodological issues identified in this review.

TABLE 3-2 : SUMMARY OF CURRENT PRACTICES AND SOLUTIONS IN ECONOMIC EVALUATIONS OF COMPANION BIOMARKERS

Methodological areas	Issues identified in the current practice of economic evaluations	Possible solutions/suggestions	
		Methodological approaches	Data requirements
Target population	Pre-selected population group with known biomarker status was targeted in EEs.	Target the entire patient group including biomarker positive, negative, and unknown.	Clinical data on all patients including false positive, false negative, unknown biomarker status.
Perspective	Payer perspective was mostly used following the HTA guidelines by the reimbursement authority.	Holistic viewpoint desired (e.g. societal perspective). However, if infeasible, biomarker testing related cost items should be included in evaluations.	-
Comparator	With versus without the use of biomarker testing compared in evaluations yet in the context of the same targeted therapy.	SOC in current routine clinical practice should be employed as a comparator in the context of treating the disease condition of interest and the target patient population.	Evidence on standard of care being routinely practiced for the target patient population with the disease condition in a country-specific setting.
Comparison structure	No consistency in structuring strategies to be compared in comparative analysis of companion biomarkers for targeted therapies.	Test-treat versus treat-all with SOC is suggested as a base-case comparison structure.	Clinical data on patients treated all with SOC without biomarker tested. Clinical data on patients tested negative.
Clinical effectiveness	Clinical value of companion biomarkers was limited to sensitivity/specificity. Often, biomarker prevalence data was ignored. Sensitivity /specificity was often assumed to be 100% or excluded completely from the economic model inputs.	Clinical value of companion biomarkers beyond sensitivity /specificity should be incorporated in economic evaluations of biomarker-guided therapies.	Clinical evidence generated from clinical trials on both the drug and the diagnostic. If possible, separate RCTs in test positive and test negative patients respectively treated with guided therapy and non-guided therapy. In addition, the clinical utility values including the change of clinician's behavior in choosing this treatment option over SOC should be captured.

Preference-based outcome	Utility and/or disutility values related to biomarker testing were not considered.	Biomarker related patient preferences should be incorporated in economic evaluations of biomarker-guided therapies.	Individual patient utility (or disutility) values on the use of a companion biomarker test prior to the administration of targeted therapy. Patient preference data can be acquired along the clinical trials, reflecting all biomarker relevant preference items.
Timing of the test use	The timing of the use of companion biomarker testing is often not incorporated and not reported in economic evaluations.	The value of companion biomarkers should be understood throughout the clinical pathways applicable to the decision-making of clinicians.	The timing of the test use in clinical routine settings is preferred over the RCT setting.
Uncertainty analysis	Many economic evaluations did not examine the characteristics of a test separately from that of the corresponding therapy.	The characteristic components relevant to a companion biomarker diagnostic should be tested separately as part of uncertainty analysis of biomarker-guided therapy.	-
Information and model inputs to be incorporated in economic evaluations of companion biomarkers	Limited number of model parameters pertinent to biomarker testing was incorporated into the economic assessment of companion biomarkers.	Model inputs relevant to companion biomarker testing should all be captured and incorporated in economic evaluations of biomarker-guided therapies.	Name/type of biomarker testing diagnostic/kit. Resource use of testing. Unit cost of testing. Capital cost if the testing device is not currently available in current clinical settings. Prevalence of biomarker status in patient population. Sensitivity/specificity. Utility and/or disutility values of performing the test in relation to preference-based outcomes. Clinical pathways including the test (for example, when the test is performed in routine clinical settings).

Many of the EEs of biomarker-guided therapies target a pre-selected patient group with a specific biomarker status instead of including all patients with a disease regardless of their biomarker status. This is then often used as a justification for excluding companion biomarker testing from EE, leading to a lack of robust economic evidence for the entire patient group with the disease. It is important to consider all patients regardless of biomarker status and then, to perform the economic assessment of companion biomarker therapies for all populations of interest with the condition or disease.

Also, EEs need to be consistent with the decision problem being addressed for targeted patient populations using a payer perspective. EEs usually adopt a perspective proposed in country-specific health technology assessment guidelines and then, the third-party payer perspective is the most frequently employed viewpoint of analysis. However, considering the multiple purposes of biomarker tests and the indirect health impact of companion biomarkers on patient outcomes of corresponding therapies, it might be better to adopt a holistic viewpoint and capture the full spectrum of health economic consequences of biomarkers. This would then permit the inclusion of non-health related costs and benefits such as early information or reassurance on treatment option.

Applying comparator strategy of relevance in specific clinical settings is crucial and may change the cost-effectiveness outcomes of the intervention being assessed. Economic evaluation of biomarker-guided therapies often requires more than one comparator arm such as biomarker-guided therapy without biomarker testing and standard of care without biomarker testing (13). A previous study (123) sometimes found conflicting cost-effectiveness results depending on the comparator strategy chosen such as test-treat versus treat-all with standard of care (SOC) and test-treat versus treat-all with new therapy. We found no consistency in the choice of comparator strategies and in structuring the

strategies to be compared. Biomarker-guided therapies are often evaluated by comparing biomarker testing and no-testing strategies in administering the new intervention being evaluated. Such comparative analyses often ignore the standard of care being provided in current clinical practice.

There are challenges in determining the clinical value of companion biomarkers. If the companion biomarkers were integrated as an integral part of the clinical trials of their corresponding therapies, determining the clinical utility of companion biomarkers can be assumed or justified that it is already reflected in the clinical effectiveness of corresponding therapies (159). Otherwise, it is difficult to show the clinical utility of companion biomarkers in clinical practice. Often, biomarker tests are developed independently from the drug and the common practice of biomarker test developers in terms of evidence generation is only limited to provide clinical validity (i.e. sensitivity and specificity). Reflecting this common practice in the generation of clinical evidence for biomarkers, we found that the assessment of the clinical value of companion biomarkers in EEs is limited to a consideration of the sensitivity and specificity of the test.

Most studies considered and included the cost of companion biomarker testing in their EEs. However, they often did not provide sufficient details on how they calculated the cost of testing and what data sources were used. This posed challenges in terms of transparency and reproducibility of EEs of companion biomarkers. This may be because testing cost is not standardized (e.g. no coding systems exist for biomarker testing in medical records) or not publicly available (e.g. secret pricing or individually negotiated price at a hospital/laboratory level) in many countries. Given that no standardized cost information such as unit costs is publicly available, most economic evaluations might need to rely on laboratory charges.

It is said in the field of precision medicine that we need to introduce more flexible reimbursement systems in order to reward innovation, reflecting the added value of diagnostics or biomarker tests (32). Otherwise, the value of biomarkers will not be fully captured and reflected in EEs. This also leads to an issue of understanding the entire clinical pathways in relation to the biomarker test and capture the right place of the added value of biomarkers in the continuum course of disease management and cure. Our study showed that many evaluations failed to reflect this aspect by not even reporting the timing of the test use. Furthermore, the patient preference utility of companion biomarkers in terms of HRQoL or adverse events was widely ignored.

CONCLUSION

It is in the public interest to ensure timely integration of new technologies into clinical use through adequate levels of reimbursement and coverage. However, it requires that test developers demonstrate robust evidence of the health economic impact of biomarker tests. Companion biomarker characteristics captured in EEs are often limited to the cost or the accuracy of the test. Often, only the costs of biomarker testing are modelled. Clinical outcomes or utilities are often difficult to include due to the limited data generated by clinical trials.

We found that there was no consistent approach applied in assessing the value of biomarkers and including the characteristics of biomarkers in an economic evaluation of targeted oncology therapies. Currently, many EEs fail to capture the full value of companion biomarkers beyond sensitivity/specificity and cost related to biomarker testing.

4. HSP27 EXPRESSION AS A NOVEL PREDICTIVE BIOMARKER FOR BEVACIZUMAB: IS IT COST-EFFECTIVE?

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	299429	Title	
First Name(s)	Mi Kyung (Kelly)		
Surname/Family Name	Seo		
Thesis Title	Economic evaluations of cancer biomarkers for targeted therapies		
Primary Supervisor	John Cairns		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	PharmacoEconomics - Open		
When was the work published?	27 January 2020		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Yes	Was the work subject to academic peer review?	Yes

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Where is the work intended to be published?	
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	
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SECTION E

Student Signature	
Date	

Supervisor Signature	
Date	29 November 2019

4.1. Research paper III

Title: HSP27 expression as a novel predictive biomarker for bevacizumab: is it cost-effective?

Authors: Mikyung Kelly Seo^{1,2}, Oddbjørn Straume^{2,3}, Lars A. Akslen^{2,3}, John Cairns^{1,2}

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Publication status: Published.

Contribution of the candidate to this paper: I conceptualised, designed and conducted this cost-effectiveness analysis. I managed the process of model input data collection and analysis (e.g. obtaining individual patient data from clinicians, obtaining cost and utility data inputs, obtaining survival data from published survival curves, conducting survival analysis, conducting receiver operating characteristic analysis, etc.). Using data inputs I obtained or analysed, I developed the partitioned survival model and conducted base-case cost-effectiveness analysis, deterministic and probabilistic analysis, and value of information analysis. I wrote the first original manuscript and revised as needed.

ABSTRACT

Background

Despite the extensive use of bevacizumab in a range of oncology indications, the US FDA revoked its approval for breast cancers, and multiple negative trials in several solid malignancies have been reported, so the need for predictive biomarkers has increased. The development of predictive biomarkers for anti-angiogenic bevacizumab therapy has long been pursued but without success.

Introduction

Heat shock protein 27 (HSP27) expression has recently been identified as a predictive biomarker for bevacizumab in treating metastatic melanoma. This study aims to evaluate the cost-effectiveness of HSP27 biomarker testing prior to the administration of bevacizumab compared to two comparator arms of treating all patients with bevacizumab and dacarbazine respectively without HSP27 testing.

Methods

A partitioned survival analysis model with three mutually exclusive health states (progression-free survival, progressed disease, and death) was developed using a Norwegian health system perspective. The proportion of patients in each state was calculated using the area under the Kaplan-Meier curve for progression-free and overall survival derived from trials of bevacizumab and dacarbazine. Three strategies were compared; 1) test-treat with HSP27 biomarker and bevacizumab, 2) treat-all with

dacarbazine without HSP27 testing, 3) treat-all with bevacizumab without HSP27 testing. Quality-adjusted life-years (QALYs) and costs (Norwegian Krone (NOK), year 2019 values) were calculated for each strategy and discounted at 4%. A life-time horizon was applied. Uncertainty analyses were performed. Expected value of perfect information (EVPI) was estimated to assess the potential value of further research to generate more evidence.

Results

Although the test-treat strategy was cost-effective compared with treat-all with dacarbazine (ICER per QALY at 21,069 NOK), it was not cost-effective compared to treat-all with bevacizumab without HSP27 testing (fewer QALYs was not justified). EVPI results showed a very minimal value (NOK 5,910 per case) or no value in conducting further research efforts to reduce uncertainties around current information.

Conclusion

This study indicates that HSP27 expression is not cost-effective as a potential predictive biomarker for bevacizumab. This may not necessarily mean that HSP27 is a bad biomarker for bevacizumab, but it may mean that bevacizumab is in any case much better than dacarbazine regardless of HSP27 expression. Or, indeed it may imply that HSP27 is not sufficiently good in identifying the right patients for bevacizumab.

INTRODUCTION

Cutaneous malignant melanoma is common in fair-skinned populations in many countries (160-163). Worldwide, 132,000 melanoma skin cancers occur each year (164). Incidence and mortality continue to rise across the world (163, 165-167). Norway has among the highest incidence of melanoma in the world (168). In Norway, the five-year relative survival is 90% for patients with localized melanoma but only 16% for those with distant melanoma (169). The target population of this evaluation followed the patient population included in a clinical trial (ClinicalTrials.gov NCT00139360); patients with metastatic melanoma. The American Joint Committee on Cancer (AJCC) staging system is internationally accepted classification system in staging patients with melanoma in stage I, II, III, IV, aligned with TNM classifications (tumor thickness, nodes, and metastasis) (170). Patients are categorized as having localized disease (stage I-II), regional disease (stage III), or metastatic disease (stage IV). Detailed classification of TNM of melanoma is provided in Appendix 4-6, followed by Schuster's PhD thesis (171).

The routinely available treatment options for metastatic melanoma were high dose interleukin-2 and dacarbazine with a low response rate of around 10% (172-174). Chemotherapy has for a long time been the main treatment option for metastatic tumours although marginally effective, with dacarbazine as the standard drug for most melanoma cases (168), being the only FDA-approved drug. However, dacarbazine has shown low response rates with no life-extending effect (168). Recently, new targeted drugs have been developed, and especially the introduction of BRAF (B-Raf proto-oncogene, serine/threonine kinase) and MEK (Mitogen-activated protein kinase) inhibitors has improved progression-free and overall survival of advanced melanoma (175-181). Biomarker-guided therapies have demonstrated considerable efficacy in the treatment of

metastatic melanoma (182, 183). Currently, the presence of a specific BRAF mutation is the biomarker recommended for routine clinical practice to administer the corresponding targeted therapies (BRAF inhibitors: vemurafenib, dabrafenib; MEK inhibitors: trametinib, cobimetinib) in advanced melanoma (182, 184-186). In addition, immune checkpoint inhibition for metastatic melanoma has created significant optimism in later years (187, 188), but no predictive biomarkers have been validated for immunotherapy. Norway has its own regulatory approval agency for medicines, called Norwegian Medicines Agency (NoMA). Norway has universal health coverage funded by general taxes and NoMA evaluates whether or not to cover the expenses of certain treatment in the national health insurance scheme (23). The reimbursement application must contain cost-effectiveness analysis data performed by the applicant (except for the application of generic products no more costly than relevant reimbursed ones) which reflects the resource use in relation to health benefit (23, 189). NoMA can make a recommendation to the Norwegian Ministry of Health concerning reimbursement of applicant's product based on an overall assessment of medical, social, and health economic information. Overall, the government plays a major role in governing the health system in Norway (190).

Given bevacizumab's mechanism of action as a vascular endothelial growth factor (VEGF) inhibitor, certain patient populations might be less likely to benefit from the drug as indicated by measured VEGF levels. Thus, a development of predictive biomarkers for bevacizumab has long been pursued but without success. Recently however, a study identified Heat Shock Protein 27 (HSP27) as a potential predictive biomarker for bevacizumab in treating metastatic melanoma (clinical trial information: NCT00139360), which is still at the early stage of a novel companion biomarker development (191). HSP27 is known to be associated with poor prognosis and treatment resistance in many cancers (192). Schuster et al. (191) suggests that 'strong' HSP27 tissue expression in melanoma

metastasis can predict response to bevacizumab. Staining intensity was defined as absent (no positive tumour cells), weak (less than 10% positive tumour cells), moderate (10-50% positive tumour cells), or strong (more than 50% positive tumour cells). The staining index (SI) is a product of intensity and area (ranging from zero to nine) (193). Based on this recent study, this cost-effectiveness analysis aims to assess the cost-effectiveness of HSP27 testing prior to the administration of bevacizumab in treating patients with metastatic melanoma. Given the early stage of companion biomarker discovery, we also aim to inform decisions to invest in further research to generate more evidence. To the best of our knowledge, there are no economic evaluations of biomarker testing prior to the administration of bevacizumab for melanoma.

METHODS

Overview

A partitioned survival analysis model (PSM), similar to previous economic evaluations of treatments of advanced or metastatic cancers, including the cost-effectiveness of a BRAF inhibitor (dabrafenib) and bevacizumab (192, 194), was developed using Microsoft® Excel® (16.0.12730.20144). Our analysis performed and reported following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (38). Model structure was conceptualized based on the decision problem of assessing the cost-effectiveness of HSP27 testing prior to the administration of bevacizumab, followed by a report from Roberts et al. (195). Provided that the disease of metastatic melanoma can be broken into mutually exclusive health states and the presence or absence of HSP27 expression can be broken into distinct states, a PSM model with three health states was chosen. This choice of

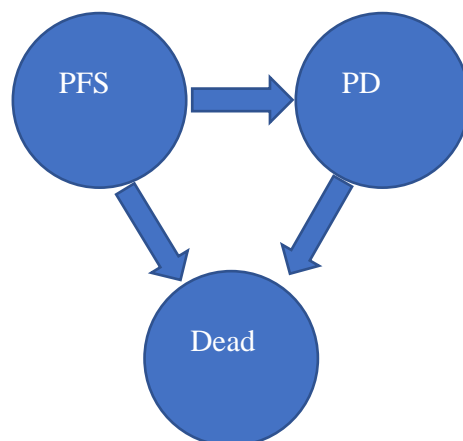
modelling type of PSM was driven by the form of available data; for example, clinical data on the comparator strategies was obtained by published Kaplan-Meier (KM) curves, which allowed to construct the model by calculating area under the KM curves.

A hypothetical cohort of 10,000 patients with metastatic melanoma was modelled. The model has three mutually exclusive health states: alive with no progression (progress-free survival, PFS), alive with progression (progressed disease, PD), or dead (Figure 4-1). The proportion of patients in each health state over time was calculated using the Kaplan-Meier (KM) survival curves for PFS and overall survival (OS). Partitioned survival analysis assumes that, at any discrete time point, the difference between the proportion of patients in OS and the proportion of patients in PFS determines the proportion of patients who are alive with PD. This PSM do not need to consider the cause of mortality and thus, all-cause mortality was not included in the dead state. Bevacizumab is not licensed for metastatic melanoma, although HSP27 expression is identified as a companion biomarker test for bevacizumab in treating bevacizumab. However, this is an early economic evaluation performed on a candidate biomarker test which is at the early stage of technology development, thereby, using clinical data from a Phase II trial for the intervention strategy (196) from the perspective of Norwegian health system considering the clinical trial was conducted on Norwegian patient population and the research interest of Norwegian funder (Centre for Cancer Biomarkers, Norway).

A Norwegian health system perspective was employed, which considered direct costs in treating metastatic melanoma. No studies have reported the prevalence of HSP27 expression for patients with metastatic melanoma in Norway. Therefore, 70% was assumed and tested in the uncertainty analysis. The model has a monthly cycle and a lifetime horizon to capture all consequences in health benefits and costs. Costs and health

outcomes were discounted at 4% annually as recommended by the Norwegian Ministry of Finance and guidelines for health economic evaluation in the health sector (197). The primary measure of cost-effectiveness was the incremental cost per quality-adjusted life year (QALY) gained.

FIGURE 4-1 : THE DIAGRAM OF HEALTH STATES INCLUDED IN THE MODEL



PFS; Progression-Free Survival, PD; Progressed Disease

Strategies compared

Three strategies were compared and assessed in this study, in treating patients either with bevacizumab or dacarbazine in the first line of MM. The intervention technology of interest in this study was testing the HSP27 biomarker status of patients prior to the administration of bevacizumab (hereafter, referred to as the test-treat strategy). This intervention strategy of interest was compared against two comparator strategies; first, treating all patients with dacarbazine without HSP27 biomarker testing (hereafter, treat-all with dacarbazine strategy), second, treating all patients with bevacizumab without HSP27 biomarker testing (hereafter, treat-all with bevacizumab strategy). This model structure follows what I found in previous chapters. Previous literature reviews found that several economic evaluations employed the modeling structure of assessing the value of biomarker-guided therapy with and without the biomarker testing. Thus, the standard of care was not considered in the economic model. It can then potentially lead to different or conflicting conclusion in terms of cost-effectiveness of a new guided therapy. Therefore, I constructed the model with three strategy arms so that the intervention strategy of HSP27

testing prior to the administration of bevacizumab can be respectively compared against all applicable comparator strategies such as treating all patients with dacarbazine without HSP27 testing (standard of care) and treating all patients with new therapy without biomarker testing.

Under the test-treat strategy, patients truly tested positive for HSP27 expression received bevacizumab while HSP27 negative patients received dacarbazine. However, for patients who falsely-tested positive, the health effect of dacarbazine was assumed for them even though they were treated with bevacizumab. Also, patients truly or falsely tested negative were assumed to be efficacious of dacarbazine because they were not treated with bevacizumab. Based on the findings of Schuster et al.(191), patients with HSP27 tissue expression with a staining index 4 or above were considered to be HSP27 biomarker positive and those below index 4 were considered HSP27 negative.

Survival estimates for partitioned survival analysis modelling

The survival analysis for bevacizumab used PFS and OS KM data from the phase II study (35 patients) (198), which identified a potential predictive biomarker to guiding administration of bevacizumab in treating patients with metastatic melanoma (MM) (191). This phase II trial is a single arm, non-randomised, non-blinded single centre study. This trial reported median OS was 9 months (mean: 13, range: 1.1-49) and the median number of cycles was 4 (mean: 14, range: 1.1-64). One treatment cycle is two weeks. This trial reported that no patients died of causes other than MM. We obtained the individual patient dataset (IPD) from the clinical research group, which reported the clinical data beyond the published trial period. We then performed non-parametric survival analysis to calculate the KM curves for OS and PFS for patients tested positive of HSP27 expression and treated with

bevacizumab. Extrapolation was required in order to incorporate non-observed survival (e.g. the event may have not occurred by the end of trial follow-up) in health economic models (199). Different distributions (exponential, Weibull, gompertz, log-logistic and log-normal) were fitted to the KM. The log-normal distribution found to be the best fit to PFS curve and the gompertz distribution for OS curve. Parameters used in fitting the parametric models were provided in Appendix 4-3. Also, KM curves and model fits were provided in Appendix 4-3 together with the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC).

Dacarbazine survival was based on the PFS and OS KM curves from the dacarbazine arm of a phase III randomized study (675 patients) (200, 201). This trial was selected based on patient characteristics such as age, ECOG performance status, and sex being broadly similar to those in the bevacizumab study (Appendix 4-1). No head-to-head trial as well as no pooled analysis (*i.e.* meta-analysis) provide a treatment effect for bevacizumab compared to dacarbazine for patients with metastatic melanoma. The OS and PFS data values were read off from the published KM survival curves using Digitizelt® (202), and the KM dataset was reconstructed using an algorithm developed in R by Guyot et al. (203); the full R code used in this study is provided in the appendix of the same paper. This process of data transformation was needed because the time-to-event data were not available. We used R version 3.5.0; R is a programming language and free software for statistical computing (204). Parametric survival distributions were fitted to the KM data reconstructed from the published KM curves using Stata (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). To determine which model best fits the data, different distributions were fitted against the data. Various distributions of exponential, Weibull, gompertz, log-logistic and log-normal were fitted and tested using AIC and BIC to determine which one best fits the data (199). The visual inspection was performed

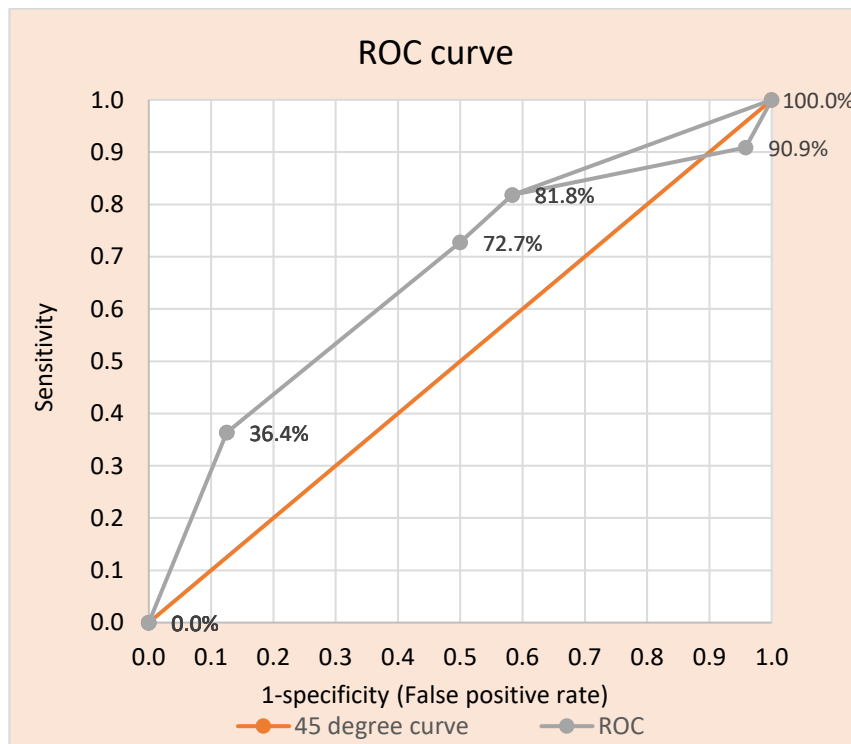
by looking at the shape of the distribution to see whether any of the models fitted appeared clearly inappropriate. To sum up, the model selection was based primarily on information criteria, supplemented by visual inspection (205). The log-normal distribution was selected for OS and the generalized gamma distribution was selected for PFS based on visual inspection, AIC and BIC. The pertinent parameters used in extrapolating survival are provided in Appendix 4-2. The log-normal distribution provided the lowest AIC and BIC values for OS and the generalised gamma distribution for PFS. AIC and BIC results are provided in Appendix 4-3.

HSP27 expression characteristics and ROC analysis

Since the HSP27 expression is still at the early stage of technology development, its performance data (e.g. diagnostic accuracy – sensitivity and specificity) was not yet estimated and thus, the receiver operating characteristic (ROC) analysis was needed in order to estimate sensitivity and specificity of HSP 27 biomarker testing. The ROC analysis was conducted, using the clinical trial data (191) in order to estimate the optimal threshold of true positive fraction and false positive fraction of HSP27 biomarker testing (206). ROC analysis is a simple but useful tool to evaluate the accuracy of a diagnostic test (207). The ROC curve shows the trade-off between sensitivity and specificity; any increase in sensitivity will lead to a decrease in specificity. The closer the curve follows the left-hand border of the ROC curve, the more accurate is the test. Meanwhile, the closer the curve comes to the 45-degree diagonal of the ROC curve, the less accurate the test is. ROC curve analysis was used to test the performance of a test in identifying eligible patients for the treatment of interest. As shown in Figure 4-2, the true positive rate (sensitivity) was plotted against the false positive rate (1-specificity) for a series of cut-off points of a parameter. It

predicted the optimal cut-off threshold of HSP27 biomarker testing performance at the sensitivity of 81.8%. Following this ROC analysis, a sensitivity of 81.8% and specificity of 41.7% have been incorporated in the cost-effectiveness model. Given the low specificity, we also considered a higher index however, when a HSP27 staining index higher than four was applied (which is staining index 6 or 9 in this case), it was worse than the random selection (45-degree diagonal of the ROC space). For example, under the HSP27 index 6, both sensitivity and specificity improved over 90%, however, it was located below the 45-degree diagonal of the ROC curve (Figure 4-2). The estimated cut-off thresholds according to different levels of the HSP27 staining indices are reported in Appendix 4-4. Thus, based on the ROC analysis results (Figure 4-2), the best cut-off threshold for determining HSP27 biomarker positivity or negativity was at the staining index 4. In other words, HSP27 expression is positive when the staining index is 4 or higher, while HSP27 negative when the staining index is lower than 4.

FIGURE 4-2 : ROC CURVE



Costs

Costs were calculated from the perspective of the Norwegian healthcare system. Direct costs included drug costs (drug acquisition and administration), HSP27 biomarker testing costs, and monitoring costs during and after the administration of drugs(197, 198, 208-211). Costs other than health care costs were not included. For the costs of testing HSP27 biomarker status, the list price of this test was used assuming 200µg/ml of HSP27 antibody and converted from USD to NOK using the exchange rate of 1USD=7.72NOK and year 2019 values used (208). The drug costs depended on the acquisition price, the dosage, and the treatment duration. The estimated cost of dacarbazine assumed that 850mg/m² body surface is administered on day 1 and then once every 3 weeks by intravenous infusion. Dacarbazine could be administered for up to 24 months while in the PFS state and then no dacarbazine given afterwards. After the 24 months of treatment with dacarbazine, monitoring costs were included for patients continuing in PFS and PD states.

Patients received 10mg/kg of bevacizumab as an intravenous infusion on day 1 of a two-week cycle until progression or for up to 12 cycles (24 weeks). Only monitoring costs were included for patients in PFS who had finished treatment after 6 months. Monitoring costs were the considered in PFS and PD states. Treatment was assumed to cease on progression. Cost calculations were made with respect to a monthly cycle length of 30.42 days. An average body weight of 80kg was assumed. The dosages used in this model follow the information in the summary of product characteristics (SPC) or trial protocol. Details of the costs are shown in Table 4-1.

TABLE 4-1 : COST INPUTS USED IN THE MODEL

Parameters		Range for SA	Reference
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	Base-case estimate	Low	High	Distribution for PSA	
Dacarbazine					
Drug acquisition cost per cycle (NOK)	1259	881	1637	Gamma	(210)
Administration cost per treatment (NOK)	1312	918	1706	Gamma	(210)
Number of doses per cycle	1.33	-	-	-	(209)
Bevacizumab					
Drug cost per mg (NOK)	415.49	291	540	Gamma	(211)
Number of doses per cycle	2	-	-	-	(198)
Average body weight(kg)	80	56	104	Normal	Assumption
Monitoring cost per cycle (NOK)	2858	2001	3715	Gamma	(210)
HSP27 testing kit (NOK)	1583	1108	2057	Gamma	(208)
Discount rate	4%	-	-	-	(197)

Health outcome (QALYs)

Quality Adjusted Life-Years (QALYs) gained were the primary health outcome of interest in this analysis. However, utility data on bevacizumab for patients in MM was not available and therefore, health state-based utility values were used in the model with the data sourced from a study which at least collected utility data on dacarbazine. The health state utility values were based on EQ-5D data collected in the BREAK-3 trial of dabrafenib vs. dacarbazine using the EuroQoL-5 Dimensions, 3 Levels instrument (212). The health state utility of patients receiving dacarbazine was 0.750. Patients treated with bevacizumab were assumed to have the same health state utility (0.767) as those receiving dabrafenib. The health state utility of all patients following progression was 0.677.

Cost-effectiveness threshold (CET)

Whether the test-treat strategy is cost-effective or not depends on how much a payer is willing to pay for additional health outcomes (QALYs or LYs) gained (213). When the intervention strategy is both cheaper and more effective than comparator strategies, it is

a dominant strategy and clearly recommended to be the optimal strategy to implement (3). However, if the intervention strategy is more effective and more expensive than comparator strategies, decision-making should be made according to the cost-effectiveness threshold (CET) set by healthcare payers. Norway does not have a specific CET however, the Ministry of Health have argued that 275,000 NOK per additional QALY gained is the best estimate of the opportunity cost of health care in Norway (214). While it is suggested that a higher CET per QALY should be accepted for more serious conditions (214), and NOK 500,000 per QALY has been used for some disease conditions, NOK 275,000 per QALY was used in this study in the absence of an explicit definition what constitutes a serious condition.

Uncertainty analysis

Sensitivity analysis: handling parameter uncertainty

We conducted deterministic sensitivity analysis (DSA) to identify key drivers in the model, whilst holding all other variables at their baseline values (213). We also performed probabilistic sensitivity analysis (PSA) to assess the uncertainty around the base case ICER by varying all relevant parameters simultaneously (215). When available, we used the bounds of 95% confidence intervals (CIs) as high and low estimates in the sensitivity analysis. When the bounds of 95% CIs were unavailable, we used a range of $\pm 30\%$. Survival estimates were based on a beta distribution. Distributions of cost inputs used for PSA are detailed in Table 4-1. Monte Carlo simulation was used to assess the effect of simultaneous variation of all relevant parameters (216). Additionally, we performed scenario analyses for sensitivity and specificity of the HSP27 expression testing to examine their impact on the cost-effectiveness results.

Expected value of perfect information (EVPI): handling decision-making uncertainty with current evidence

Healthcare decisions made based on existing information have the costs of uncertainty. If the wrong decision is made based on existing information, there will be opportunity costs in terms of healthcare resources and health benefits. The expected costs of uncertainty can be interpreted as expected value of perfect information (EVPI) because perfect information can remove the possibility of making wrong decisions (217). The opportunity costs of making wrong decisions can be estimated using the value of information techniques. The EVPI estimates the upper bound of the value of conducting further research, meaning that additional research cost is not justifiable if the expected cost of future research does not exceed the research cost (218).

EVPI estimated the expected value of a decision made with current information against perfect information (Equation 1).

$$\text{Equation 1. } EVPI = E_{\pi}[\max_t NB(t, \pi)] - \max_t E_{\pi}[NB(t, \pi)]$$

Where;

π refers to unknown parameters, NB the net benefit, t the treatment, $NB(t, \pi)$ the net benefit of treatment if parameters take the value π .

RESULTS

Deterministic cost-effectiveness results

The base-case ICER per QALY for the test-treat strategy (Bevacizumab plus HSP27 testing) compared to treat-all patients with dacarbazine without HSP27 testing was NOK 21,069, being cost-effective. However, the test-treat strategy was not cost-effective when compared to treat-all with bevacizumab without HSP27 testing because it costed less and produced fewer QALYs (Table 4-2). To be cost-effective in this situation, the ICER needs to be above the CET. Otherwise, the cost saving is not compensating adequately for the loss of benefit. In other words, we should be able to save costs per QALY at a rate above the CET, otherwise, it is not worth giving up the QALYs and we would rather keep the QALYs. The base-case ICER results clearly showed lower than the Norwegian CET (NOK 275,000).

TABLE 4-2 : DETERMINISTIC AND PROBABLISTIC COST-EFFECTIVENESS RESULTS

Strategy	Life years (LYs)	QALYs	Incr LYs	Incr QALY	Costs (NOK)	Incr costs (NOK)	ICER (per LYs)	ICER (per QALY)	Net health benefit
Deterministic results									
Treat-all strategy with DTIC	4.11	2.92		-	1,482	-			
Test-treat strategy (HSP27 + Bmab)	11.23	8.25	7.11	5.33	113,857	112,374	15,795	21,069	4.88
Treat-all strategy with Bmab	14.09	10.36	2.86	2.11	146,583	32,727	11,429	15,515	2.05
Probablistic results									
Treat-all strategy with DTIC	4.11	2.91		-	1,598	-			

Test-treat strategy (HSP27 + Bmab)	12.05	8.89	7.94	5.98	132,148	130,550	16,439	21,847	5.45
Treat-all strategy with Bmab	14.11	10.36	2.05	1.47	151,427	19,279	9,387	13,151	1.41

Bmab; bevacizumab, DTIC; dacarbazine, HSP27; heat shock protein 27, ICER; incremental cost-effectiveness ratio, Incr; Incremental, NOK; Norwegian Krone, QALY; quality-adjusted life years.

Probabilistic cost-effectiveness results

The probabilistic cost-effectiveness results showed that the total cost and QALYs gained for individuals tested for HSP27 and treated with bevacizumab were NOK 132,148 and 8.89 QALYs, where those patients simply treated with dacarbazine were NOK 1,598 and 2.91 QALYs, respectively (Table 4-2). Therefore, the ICER per QALY was NOK 21,847.

However, the test-treat strategy was not cost-effective when compared with the treat-all with bevacizumab strategy. It saved costs but produced fewer QALYs as observed in base-case results. Likewise, the cost savings per QALY needed to be at a rate above the CET in order for the intervention strategy to be cost-effective. However, the ICER per QALY is NOK 13,151 which was far below the Norwegian CET.

Sensitivity analysis results

Tornado diagram

The DSA results are presented in a tornado diagram (Appendix 4-5). The key drivers in the model were the bevacizumab costs and the proportion of HSP27 positive patients. However, they did not ultimately change the cost-effectiveness decision.

Probabilistic sensitivity analysis

PSA was performed to assess the effect of parameter variation across all relevant parameters on the base-case ICER when all parameters simultaneously varied. One thousand simulations were run with QALYs gained as effectiveness measures.

The scatterplot of the incremental costs and incremental QALYs from these simulations are presented in Figure 4-3 and Figure 4-4. All the iterations were contained in the north east quadrant of Figure 4-3 which means that the test-treat strategy of bevacizumab and HSP27 biomarker testing was costlier and more effective than the strategy of treating all patients with dacarbazine without HSP27 testing. However, when the test-treat strategy was compared to the strategy of treat-all with bevacizumab, a majority of the 1000 simulations were located in the southwest quadrant of the scatterplot, suggesting that the intervention strategy was less costly but less effective as well (Figure 4-4). The PSA results confirmed that, although the test-treat strategy was cost-effective compared to treat-all with dacarbazine, it was not cost-effective compared to treat-all with bevacizumab without HSP27 testing, and base-case results being robust to changes in all variables.

FIGURE 4-3 : PSA SCATTERPLOT FOR TEST-TREAT STRATEGY COMPARED TO TREAT-ALL WITH DACARBAZINE

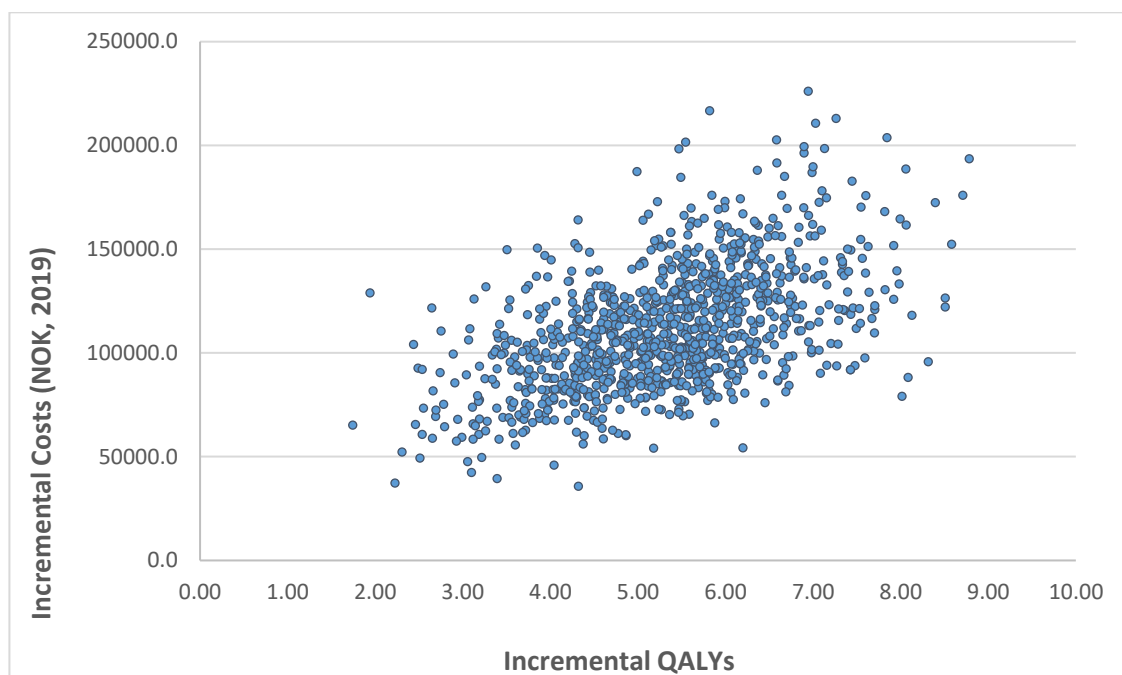
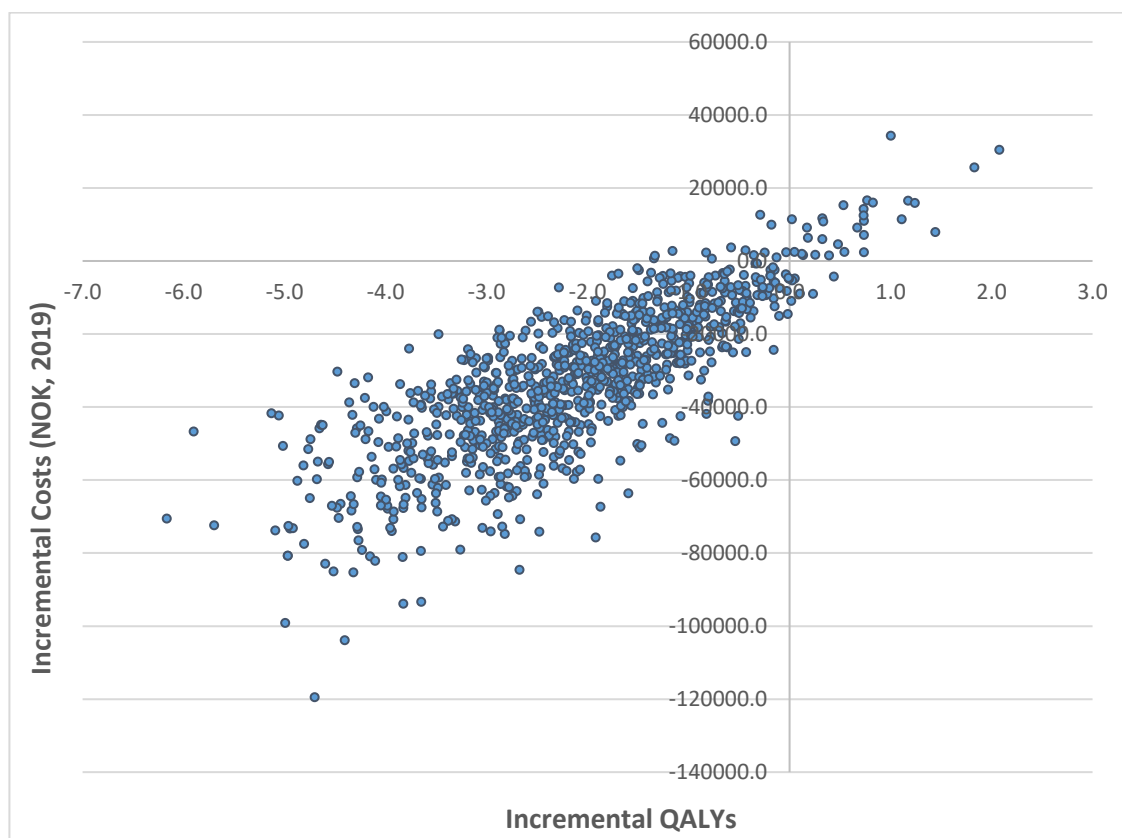


FIGURE 4-4 : PSA SCATTERPLOT FOR TEST-TREAT STRATEGY COMPARED TO TREAT-ALL WITH BEVACIZUMAB



Scenario analysis on the sensitivity and specificity of HSP27 expression testing

Scenario analysis was performed to examine the impact of the sensitivity and specificity of HSP27 testing on the cost-effectiveness results. It did not change the results in the different scenarios of the sensitivity and specificity of HSP27 testing under the different staining index of HSP27 expression. The cost-effectiveness results depending on different combination scenarios of sensitivity and specificity of HSP27 expression testing is provided in Figure 4-4.

TABLE 4-3 : SCENARIO ANALYSIS RESULTS

HSP27 staining index*	Sensitivity	Specificity	ICER per QALY (NOK, year 2019)	
			Test-treat strategy against treat-all with dacarbazine	Test-treat strategy against treat-all with bevacizumab
8	36.4%	12.5%	36737	11453
6	72.7%	50.0%	22634	13989
4	81.8%	58.3%	21069	15515
3	90.9%	95.8%	19818	18234
2	100%	100%	18794	24450

*HSP27 expression is positive when the staining index ≥ 4 and HSP27 negative when the staining index < 4 .

EVPI analysis results

A willingness-to-pay of NOK 275,000 was assumed in the EVPI analysis. The EVPI was estimated at NOK 5,910 for the test-treat strategy vs. treat-all with bevacizumab, while the EVPI was estimated at zero value for the comparison of the test-treat strategy and treat-all with dacarbazine (Table 4-5). The EVPI for the test-treat strategy against the treat-all with dacarbazine implies that further research to reduce the uncertainties around current information would not be warranted. Likewise, the EVPI of NOK 5,910 for the test-treat strategy against the treat-all with bevacizumab implies further research might not be

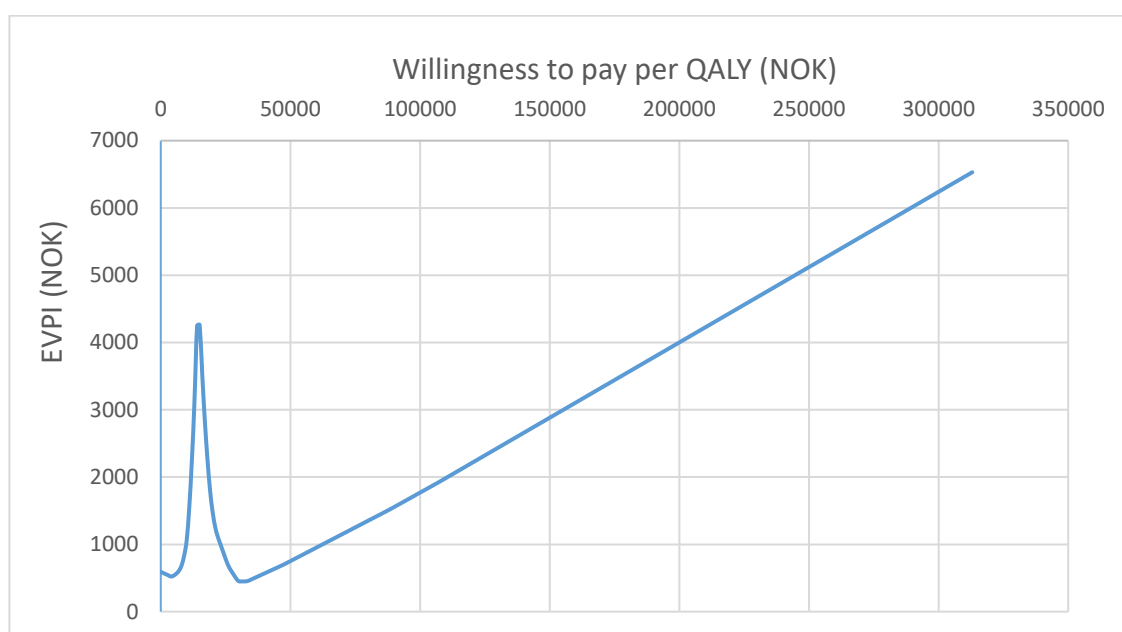
worthwhile either, given the small number of new cases of metastatic melanoma in Norway (annual average of 173 cases (169)). The upper bound of the population EVPI of the comparative analysis between the test-treat and the treat-all bevacizumab strategy was only NOK 1,022,430 per annum (EVPI per patient multiplied by the annual case of MM in Norway). In other words, in order to justify further investment in research efforts of data collection such as conducting a phase III trial for HSP27 testing and bevacizumab, the research costs need to be lower than this upper bound, which is very unlikely for Norway. However, a couple of data limitations should be considered when interpreting this EVPI result. First, we need to consider that this analysis is based on a single arm study with the small sample size (35 patients) for bevacizumab-related strategy arms. However, according to Schuster et al. (198), a statistical significance of their study results was met despite its small sample size. Second, considering the nature that this analysis was conducted using the clinical inputs from the Phase II trial, the interpretation of this EVPI result can be considered exploratory rather than definitive. EVPI results are provided in Table 4-5. The EVPI graph depicted in Figure 4-5: EVPI graph. Figure 4-5 shows the change of EVPI depending on different thresholds. The spike is when we have maximum uncertainty where CET equals the ICER.

TABLE 4-4 : EVPI RESULTS

ENMB for test-treat Strategy (NOK)	MNB for treat-all with dacarbazine (NOK)	Max mean (NOK)	Mean max (NOK)	EVPI (NOK) per patient
2474879	910986	2474879	2474879	0
ENMB for test-treat strategy (NOK)	MNB for treat-all with bevacizumab (NOK)	Max mean (NOK)	Mean max (NOK)	EVPI (NOK) per patient
2464076	3097583	3097583	3103493	5910

ENMB; Expected net monetary benefit, NOK; Norwegian Krone

FIGURE 4-5: EVPI GRAPH



EVPI; expected value of perfect information, NOK; Norwegian Krone, QALY; quality-adjusted life year.

DISCUSSION

The cost-effectiveness of giving bevacizumab in treating MM to those testing positive for HSP27 was compared with two alternative strategies (treating all patients with bevacizumab without HSP27 testing and treating all patients with dacarbazine without HSP27 testing), using a partitioned survival model. From the Norwegian health system perspective, a strategy of HSP27 biomarker testing was not cost-effective. Treating all patients with bevacizumab was the best of the three strategies. EVPI results suggested that investing in further research of evidence generation, such as a Phase III trial, is not justified given the number of patients with metastatic melanoma in Norway. This is the first study analysing the cost-effectiveness of HSP27 biomarker testing prior to the administration of bevacizumab. There are no cost-effectiveness analyses of potential biomarkers (newly discovered yet unregistered for routine clinical use) in metastatic melanoma.

Previous studies have assessed the cost-effectiveness of BRAF and MEK inhibitors in metastatic melanoma. They employed a variety of different modelling approach, ranging from decision tree analysis, to PSA and Markov model. Delea et al. (194) employed a PSA similar to my study and evaluated the cost-effectiveness of BRAF inhibitors however, did not assess the impact of BRAF testing separately. Tarhini (219) used a discrete event simulation model and assessed the sequence of different targeted therapy options in melanoma but biomarker status was not considered. Curl and her colleagues (220) also estimated the cost-effectiveness of treatments for BRAF-mutated metastatic melanoma patients, using decision tree model. Likewise, Bohensky (221) conducted the cost-effectiveness for the treatment of BRAF wild-type advanced melanoma in Australia based on a Markov model, but all patients entering the model were BRAF-wild-type. However, none of these studies analysed the cost-effectiveness of biomarker testing prior to the provision of corresponding targeted therapies. However, Oh and her colleagues (222) analysed the cost-effectiveness of targeted therapy depending on the biomarker status (PD-L1 positive and negative patients) and found that PD-L1 biomarker status contributed the most uncertainty to their model. However, none of these previous studies were performed from the perspective of Norwegian health system based on Norwegian populations.

This study has several limitations. First, the survival data for dacarbazine is derived from one clinical study not through meta-analysis. No meta-analysis study on the effect of dacarbazine was found and thus, we chose a study based on the patient characteristics in clinical trial among other studies considered for dacarbazine monotherapy for patients with metastatic melanoma (223, 224). On the other hand, the survival data for HSP27 testing and bevacizumab was derived from a small-sized single arm non-randomised study (NRS), although a randomised trial (RT) is the preferred study design to generate clinical

evidence for health interventions. We thus need to consider that potential biases are likely to be greater for non-randomised trial (NRT) compared to RT such as selection bias and confounding. In other words, in NRT, the observed difference in treatment effects between intervention and control groups might be due to differences in baseline characteristics of patients and not necessarily the treatment (225). However, RT study is not always feasible for early stage health technology and is costly in money and time (226). Furthermore, this is the only clinical data available on HSP27 expression and bevacizumab for patients with metastatic melanoma. Second, bevacizumab does not have a marketing authorization for treating patients with metastatic melanoma. This might limit the usability of this study finding in informing decision-makers when reviewing the introduction of this new companion biomarker test prior to the administration of bevacizumab in MM. However, the objective of this study is to determine the value of HSP27 testing in terms of cost-effectiveness and EVPI. Third, given the early stage of the development of HSP27 biomarker for bevacizumab, it was necessary to make some assumptions with regard to HSP27 testing. Fourth, it is a naïve indirect comparison and we did not perform matching patients between dacarbazine and bevacizumab. This may lead to some potential bias in the results. For example, patients in dacarbazine trial were younger than those in bevacizumab trial; however, the eastern cooperative oncology performance (ECOG) status was better for patients in bevacizumab trial than for those in dacarbazine. Also, it is known that the prognosis of female patients with MM is better than that of male patients with MM. However, both trials showed the same proportion in male and female population. Fifth, the utility values were not available on patients with MM treated with bevacizumab for Norwegian populations. However, utility values on patients treated with dacarbazine were available and also, the model applied utility values for a targeted therapy for patients treated with bevacizumab. A separate systematic review was not conducted to collect or

synthesise the utility data in order to complete this PhD research within the timeline. However, the objective of this work package is to apply the previous study findings (Chapter 2 and 3) in a case study of modelling a novel companion biomarker test for targeted cancer therapy. Sixth, all-cause mortality was not modelled in this analysis. It was assumed that no patients died of causes other than MM in this model given that patients entering the model are already at the metastatic stage of melanoma (short survival). Clinical data extracted from published KM curves did not differentiate all cause death from disease specific. Furthermore, Schuster and colleagues (198) in fact reported that no patients in their trial died of any causes other than MM.

CONCLUSION

The cost-effectiveness results showed that testing HSP27 biomarker status prior to the administration of bevacizumab was not cost-effective. The finding may imply that this HSP27 biomarker is not good enough in identifying the right patients for treatment as shown in the results of ROC curve analysis, or that bevacizumab is in any case much better than dacarbazine in terms of health outcomes regardless of identifying eligible patients or not. The EVPI suggests that no further research is required to generate more evidence for assessing the test-treat strategy against the treat-all with dacarbazine; however, it suggests some health gains to reduce the uncertainties around the comparative analysis of test-treat strategy and treat-all with bevacizumab strategy. Depending on the budget required to conduct further studies such as clinical trials, the decisions regarding additional research efforts can be reasonably determined by Norwegian stakeholders by taking into

account of the expected gain in health and the upper bound of the monetary value of perfect information as suggested by EVPI.

5. A PRACTICAL GUIDE TO CONDUCTING A COST-EFFECTIVENESS ANALYSIS OF CANCER BIOMARKERS FOR TARGETED THERAPIES: TUTORIAL

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	299429	Title	
First Name(s)	Mi Kyung (Kelly)		
Surname/Family Name	Seo		
Thesis Title	Economic evaluations of cancer biomarkers for targeted therapies		
Primary Supervisor	John Cairns		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

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Where is the work intended to be published?	
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	
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SECTION E

Student Signature	
Date	

Supervisor Signature	<i>John Cairns</i>
Date	<i>29 November 2019</i>

5.1. Research paper IV

Title: A practical guide to conducting a cost-effectiveness analysis of cancer biomarker for targeted therapy

Author: Mikyung Kelly Seo

Affiliations: ¹ Department of Health Services Research and Policy, Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom. ² Centre for Cancer Biomarkers (CCBIO), University of Bergen, Bergen, Norway.

Contribution of the candidate to this paper: As a sole author, I designed and developed the health economic model and wrote the R code. I led the entire process of developing this core model and wrote the paper. However, I acknowledge that I have received technical advice in writing R code from Dr. Nichola Naylor, Prof. Mark Strong, and Dr. Fernando Alarid Escudero. I also acknowledge that my PhD supervisors, Professor John Cairns and Dr. Alec Miners have provided comments on this paper.

ABSTRACT

Despite the increasing number of potential biomarkers identified in laboratories and reported in much literature, the number of biomarkers routinely adopted in clinical use is very limited. Reimbursement decisions for new health technologies are often informed by economic evaluations. It is argued that the lack of consensus in methodological approaches and data requirements in economic evaluations of biomarkers might be one of the key limiting factors on why there are yet only a small number of biomarker tests routinely provided in clinical practice. This paper provides practical guidance on how to conduct

economic evaluation of cancer biomarkers and how to model the characteristics of cancer biomarkers as part of the value for money of corresponding targeted therapies. This paper presents a brief introduction to the methods and data requirements, a step-by-step guide to constructing a health economic model of cancer biomarkers, and a discussion of issues that arise in their application to healthcare decision making. This practical guidance is provided in R, and worked examples are provided in this paper with R codes in accompanying appendices.

INTRODUCTION

This tutorial paper aims to guide the process of the development of cost-effectiveness models of cancer biomarkers for targeted therapies (i.e. specifically companion diagnostics, classifying patients into responders and non-responders for a specified therapeutic agent in treating patients with cancer). Although model conceptualization is the first key step in developing an appropriate model, it is beyond the scope of this tutorial paper. This paper is intended for those who chose a state-transition model as their appropriate model based on their decision problems to be represented in the model. For those who are not yet clear what model types are appropriate for their decision problems, there is a useful paper providing a series of consensus-based best practices for the process of model conceptualization (195). For example, when the decision problem requires modelling the effect of patient interaction (e.g. the treatment effect on disease spread), this core model is not applicable. As explained in Roberts et al.(195), this state-transition model is appropriate in where the disease is broken into distinct health states, as in cancer.

This core model can be applied in assessing cancer biomarkers for targeted therapies in terms of data requirements and methodological approaches for the purpose of local adaptation with appropriate adjustments required from the perspective of specific payers and country settings. The example used in this tutorial paper has three health states, progression-free survival (PFS), progressive disease (PD), and dead. This analysis is performed for a hypothetical cohort of cancer patients who are not eligible for tumor excision surgery.

I chose to use R in building this practical model because of the advantages of using R (or script-based programming) for the development of economic models for health technology assessment although these are only beginning to be recognised (227). R is easily reproducible and flexible compared to Excel®.

MODEL BACKGROUND AND DESCRIPTION

Overall, several elements need to be defined in order to construct the health economic model for health technologies. The scope and scale of the relevant decision problems are presented in Table 5-1, using the PICOS framework. The decision problem is basically to assess the cost-effectiveness of testing patients with a companion biomarker test and treating them according to their biomarker status, in comparison with comparator strategies such as treat-all patients with the biomarker-guided therapy or treat-all patients with usual treatment regardless of biomarker status without testing. The study design is model-based cost-effectiveness analysis using a hypothetical cohort of patients and the study outcome to be calculated is ICER (cost per LY and cost per QALY gained). The reference case applied in this worked example of the core model is summarised in Table 5-

2. This core model is developed based on the findings of Chapters 2-4. The process of building a health economic model involves defining the structure of the model and data inputs. Its detailed descriptions are provided in sub-sections as follows.

Table 5-1 : Scope of decision problems

Population	A hypothetical cohort of patient populations with cancer.
Intervention	Companion cancer biomarker testing* for co-dependent therapeutics such as biomarker-guided therapies.
Comparators	Biomarker-guided therapies without biomarker testing. Usual therapies without biomarker testing.
Outcome	ICER, ICUR
Study design	Economic evaluation; model-based cost-effectiveness analysis.

* Companion diagnostics licensed for the safe and effective use of specific drug or biological product.

TABLE 5-2 : SUMMARY OF THE REFERENCE CASE USED IN THIS GUIDE

Element	Reference case
Intervention strategy	Test-treat patients according to biomarker status, using companion diagnostics for targeted therapies.
Choice of treatment alternative (comparator strategies)	The comparator strategy that the new biomarker-guided therapy will most likely to replace. Thus, in this core model, two comparator strategies employed: 1) Treat-all patients with biomarker-guided therapy regardless of biomarker status; 2) Treat-all patients with usual treatment regardless of biomarker status.
Health state	Three health states: Progression-free survival (PFS), Progressed disease (PD), Dead
Viewpoint of the analysis	Health system perspective
Time horizon	Lifetime
Model of analysis	Cost-utility analysis
Health outcome	Quality adjusted life year

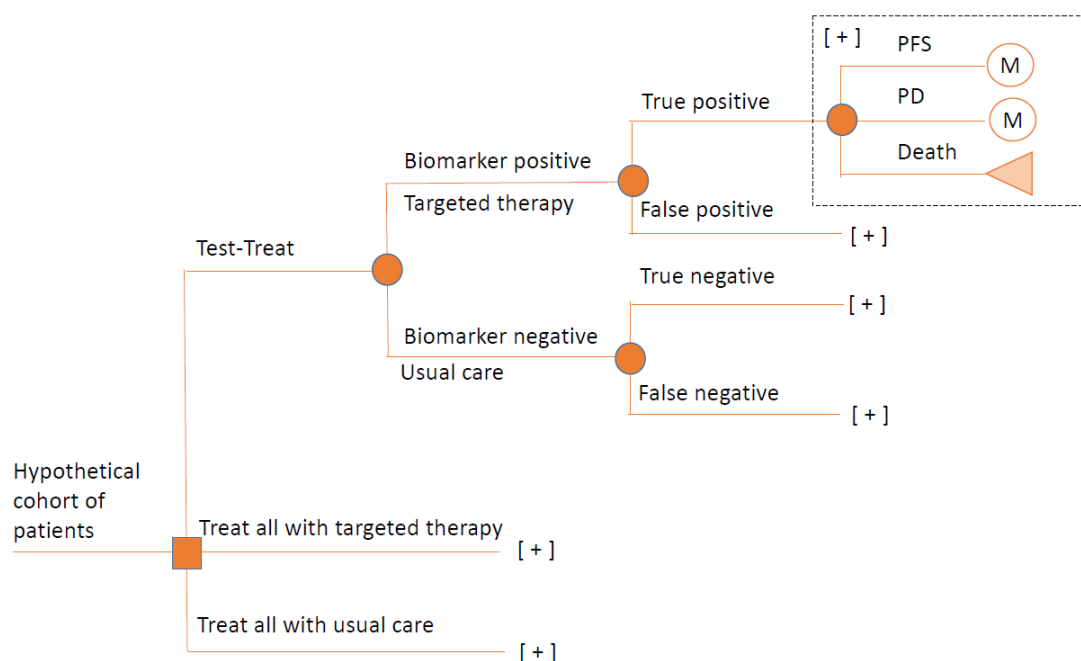
Method for the measurement and valuation of health effects	Generic measures of health instruments
Discounting rate	3.5%
Uncertainty	Probabilistic sensitivity analysis; with an option of deterministic sensitivity analysis

Strategy arms to be compared and assessed

It is widely accepted that standard of care (SOC) is an appropriate comparator strategy in economic evaluations (3). However, my literature reviews (Chapters 2,3) found that the existing literature of economic evaluations demonstrates that the choice of comparator strategies and the comparison structure is not consistently applied in economic evaluations of biomarker-guided therapies. For example, SOC (e.g. usual therapy without biomarker testing) was not necessarily chosen as a comparator strategy but evaluated the cost-effectiveness of biomarker-guided therapy with testing against the guided therapy without biomarker testing. Therefore, based on the study findings from Chapters 2-4, it was found that assessing the biomarker-guided therapy against two comparator strategies was most commonly relevant. However, this core model allows readers to alter this structure of comparative analysis for their decision-specific problems and local requirements in economic evaluations. In this core model, I constructed the model structure using three strategies so that it can ensure the flexibility and applicability of this core model for readers to readily adapt. The three strategies constructed in this core model as default structure as follow: (1) patients being tested with a cancer biomarker and treated with the corresponding targeted therapy according to the biomarker testing result (hereinafter, test-treat strategy; “TT arm”), (2) a usual care strategy with patients being treated with standard of care without testing of their biomarker status (hereinafter, usual care strategy; “all-UC arm”), (3) a targeted care strategy where patients are not tested but

receive the biomarker-targeted therapy (hereinafter, targeted care strategy; “all-TC arm”). This construct of comparative strategy arms is also line with what has been suggested by previous studies (13, 122). The detailed schematic of comparative structure of strategy arms is depicted in Figure 5-1.

FIGURE 5-1 : MODEL SCHEMATIC. ‘M’ INDICATES A MOVE INTO THE MODEL IN FIGURE 5-2

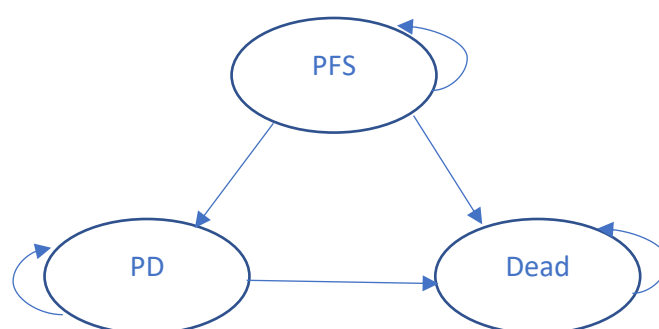


Model structure

A discrete-time Markov cohort model is constructed to record the transition between health states experienced by a hypothetical cohort of patients eligible to be treated either with targeted care (biomarker-guided therapy) or usual care (non-guided therapy) in oncology treatments. Health-related quality of life weights and a cost pertinent to each of these health states are assigned. The model has three mutually exclusive health states: progression-free disease (PFS), progressed disease (PD), and dead. As depicted in Figure 5-2, the arrows indicate the flow of individual patients in every model cycle. Transition from PD to PFS is assumed to be impossible. The transition probability can be calculated using the formula suggested by Briggs (213). Given that health states are mutually

exclusive, the transition probabilities sum to one. A Markov model of disease progression is presented in Figure 5-2. The detailed model schematic of decision tree linking to the health state transitions is provided in Figure 5-1, and 'M' indicates a move into the Markov model. Once patients are allocated to their respective decision branch, they will enter a Markov model based on their assigned transition probabilities. Patients assigned to 'treat-all' strategies (either with new therapy or with usual therapy) will enter the Markov model without being biomarker-tested and move to respective health states (PFS, PD, Dead) assigned by given transition probabilities. On the other hand, patients assigned to 'test-treat' strategy arm will be either provided of new therapy or usual therapy according to biomarker status and then will enter a Markov model and assign to respective health state followed by transition probabilities. A lifetime horizon is applied.

FIGURE 5-2 : HEALTH TRANSITION DIAGRAM



PFS; progression-free survival, PD; progressed disease.

Data requirements and model inputs used in the practical/example model

Model inputs are detailed in Table 5-3. These data inputs are just exemplary figures to guide the process of developing an economic model for biomarker-guided therapies, developed based on the previous study findings (Chapter 2 to 4). A third-party payer perspective (e.g. the National Health Service) is employed in developing the model and

thus, any non-medical costs (e.g. lost productivity costs) are beyond the scope of this core modeling practice. Health state costs are defined per model cycle including drug costs and biomarker testing costs (Table 5-3). Health-related quality of life (HRQoL (e.g. EQ-5D)) data inputs are also provided in Table 5-3. In practice, HRQoL data is often obtained along with clinical trials or by separate literature reviews (e.g. systematic literature review and/or meta-analysis). However, for the development of this practical guide on core modeling for cancer biomarkers, HRQoL weights are given per model cycle for patients experiencing each health state. Biomarker-related parameters such as biomarker testing disutility value, performance accuracy (sensitivity and specificity), and biomarker prevalence are also shown in Table 5-3. Companion diagnostic technology for cancer patients usually require collecting a bio-sample for analysis, and this gives rise to the existence of process utility (such as reassurance or information) (151-153) Brennan and Dixon supported the existence of process utility and found that different approaches being used to detect and measure it (154). Given the existence of process utility, in this core model, testing disutility was used under the assumption that undergoing biomarker testing might cause some discomfort to patients. However, if this is not the case (e.g. testing bring not discomfort but convenience to patients), the utility value of testing should be considered when adapting this core model. In addition, transition probabilities, drug efficacy and discounting rate are also provided. All-cause mortality was not considered into this core model however, it should be considered when adapting this core model for local adaptations of country specific settings. In other words, modelers are advised to incorporate the country specific epidemiological data such as all-cause mortality into the core model for their local adaptations if applicable.

TABLE 5-3 : PARAMETER VALUES FOR THE MODEL DEVELOPMENT

Name	Value	Description
------	-------	-------------

Costs		
cPFS	500	State cost of one cycle in the progression-free disease state.
cPD	3000	State cost of one cycle in the progressive disease state.
cDrug	1000	State cost of drug for one cycle.
cTest	100	State cost of biomarker testing for one cycle.
cDead	0	State cost of one cycle in the death
Quality of life adjustments		
uPFS.UC	0.75	Quality-of-life weight for one cycle in PFS for patients treated with usual care.
uPD.UC	0.65	Quality-of-life weight for one cycle in PD for patients treated with usual care.
uPFS.TC	0.80	Quality-of-life weight for one cycle in PFS for patients treated with targeted care.
uPD.TC	0.70	Quality-of-life weight for one cycle in PD for patients treated with targeted care.
Biomarker-related parameters		
disutility.Test	0.05	Disutility value of testing a biomarker status
pSensitivity	0.95	Biomarker testing accuracy: Sensitivity
pSpecificity	0.75	Biomarker testing accuracy: Specificity
pPrevalence	0.35	Biomarker prevalence/frequency
Transition probabilities		
pPFS2PD	0.2	Probability of entering the PD state.
pPD2D	0.25	Probability of dying from the PD.
pPFS2D	0.05	Probability of dying from the PFS.
pPD2PFS	0	Recovery from PD to PFS is not permitted in the model.
Other parameters		
eff	0.25	Targeted drug reduces likelihood of being progressed by 25%. Relative risk of disease progression from using the drug. Targeted drug is discontinued upon progression.
rDiscount	0.035	Discount rate for outcomes and costs 3.5%

Uncertainty analysis

Uncertainty analysis is a standard practice in modeling studies to assess the uncertainties around parameters and assumptions used in the model. Both deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) are performed in this practical model in order to assess the impact of different variables on the cost-effectiveness results. DSA is performed to test the change of ICERs while individual parameters are changed from maximum to minimum range of values. As for PSA, all parameters are simultaneously

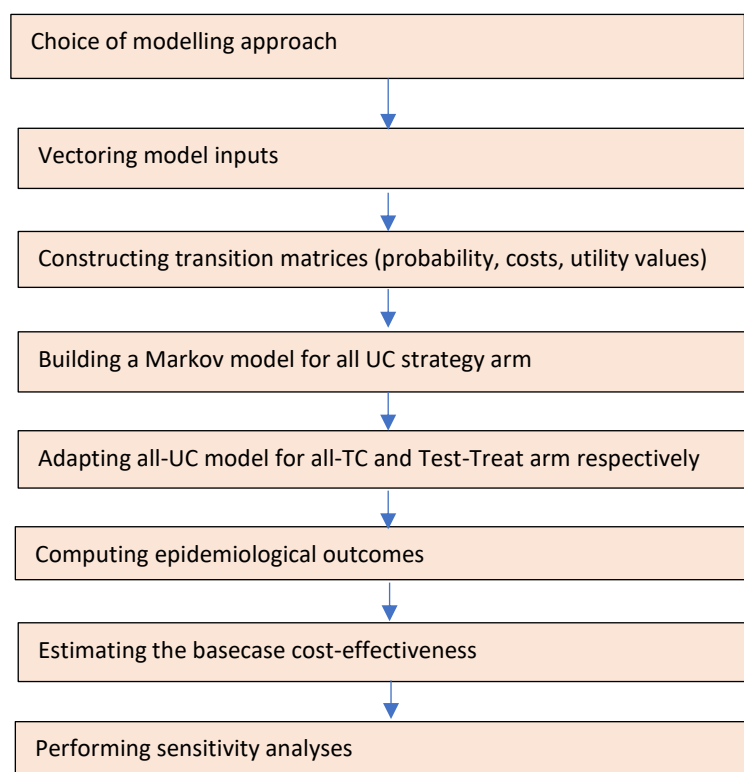
tested for uncertainty while randomly sampling the parameter values according to the assigned distribution data.

STEP BY STEP GUIDE

Figure 5-3 is an overall picture of the steps involved in order to perform cost-effectiveness analysis of cancer biomarkers for targeted therapies in R. Note that it is a general guidance and thus, some specific adjustments might be required depending on the country specific clinical settings or country specific HTA requirements. It should be also decision problem specific. An explanation of each step is provided. More detailed R codes are provided in Appendix 5-1 to 5-7. R codes can be self-explanatory with some notes written in italics with the symbol of # which can be useful when the codes are copied and pasted in R; however, basic understanding on R is required in order to follow this guide. This modeling guide is not intended for complete R beginners. For a basic note, the symbol of <- is to assign values in R.

FIGURE 5-3 : ALGORITHM STEPS IN PERFORMING COST-EFFECTIVENESS ANALYSIS FOR CANCER

BIOMARKERS FOR TARGETED THERAPIES IN R



Step 1. Create transition probability matrices

The step is to prepare the transition probability matrix per strategy arm. Before this step, it is necessary to decide first what model is suitable such as a Markov or semi-Markov model, etc. as shown in Figure 5-3. This core model presented here is constructed based on a state-transition model. In order to construct the probability matrices, parameter values exemplified in Table 5-3 need to be assigned to R first. It can then create the transition matrix of each health state per strategy arm. Refer to

Appendix 5-1 for the entire R code for this step 1.

Step 2. Create cost and utility transition matrices

Similarly, the transition matrices for cost and utility values can be prepared using the command of Matrix in R. This step is similar to step 2 in a sense that model inputs are defined and vectored into the R model. The detailed R code for this step 2 is provided in Appendix 5-2.

Step 3. Building a Markov model for all-UC arm

Based on the transition matrices set up in the step 1, a Markov trace which a hypothetical cohort of patients summing up over time needs to be constructed. In this stage, all different scenarios of treatment pathways by different strategy and testing results should be respectively constructed as depicted in Figure 5-1 and 5-2. Thus, biomarker related data need to be defined and vectored into the R model including biomarker testing accuracy and biomarker prevalence. 1000 cycles were assigned to capture the lifetime horizon of all patients entered in the model and one cycle is a month in this core model. In other words, 1000 cycles are equivalent to 83.33 years which is long enough to simulate the model in a lifetime horizon. Depending on the progression of disease of interest, the cycle can be shortened or lengthened. These model settings can be easily altered according to local adaptation requirements. R code for this step 3 is detailed in Appendix 5-3.

Step 4. Adapting the model for all-TC arm and Test-Treat arm respectively

This stage is relatively simple. The R code used for all-UC arm in step 3 can be easily modified and adapted for both the all-TC and TT arms. This feature is one of the advantages of using a script-based program when building health economic models. It can be easily transformed and adapted for other strategy arms with relatively small efforts and time

dedicated. The cohort trace of patients in the all-TC arm needs to be separated into two branches depending on their actual biomarker status because all patients will be treated with biomarker-guided therapy however, some of the patients might not be biomarker positive and thus the targeted therapy will not be effective for them. The cohort trace for the patients in the TT arm needs to be separately constructed for patients truly-tested positive, falsely-tested positive, truly-tested negative, falsely-tested negative. Cohort simulation commences with a hypothetical cohort of patients (in this core model, it is set at 1000; which means a hypothetical cohort of 1000 patients started the model) These patients then move or stay in the possible health state according to the transition probabilities defined by different treatment scenarios of strategy arms. The simulation tracks the cohort from one cycle to the next following the transition probabilities. Refer to Appendix 5-4 for the detailed R code of this step 4.

Step 5. Computing epidemiological outcomes

Epidemiological outcomes of different health states can be computed and plotted in a graph using the R code written in Appendix 5-5. Respective cohort trace per strategy arm can be plotted as survival curves. For all-TC arm and TT arm, the matrices of cohort transition need to be merged before plotting survival curves. Overall survival (OS) probability can be separately computed and plotted in OS curve according to different strategy arms. Life expectancy can be calculated by summing probability of OS over time.

Step 6. Estimating the base-case cost-effectiveness

It is now ready to perform the analysis and estimate the expected values and cost-effectiveness. In R, the expected values of each strategy can be calculated by processing the multiplication of the Markov trace produced in Step 3 and 4 and the transition matrices of cost and utility inputs produced in Step 2. The R code for this step 6 is provided in Appendix 5-6 with self-explanatory comments in italics. The example base-case ICER calculated for this exercise is also provided in Appendix 5-6.

Step 7. Performing sensitivity analyses

Given that there is uncertainty around parameter values used in the analysis, the base-case ICER results are left with a question how much confidence can be placed on the results. Sensitivity analysis is used to investigate the impact of uncertainty. By testing the impact of parameter uncertainty for example on the base-case results, decision makers can determine the confidence to be placed on decisions based on the health economic modeling analysis. Uncertainty analysis is a standard practice in modeling studies in order to assess the uncertainties around parameters and assumptions used in the model. Traditionally, researchers reported a range of parameters to assess the impact by altering a single parameter value (one-way sensitivity analysis) or a combination of parameters (scenario sensitivity analysis) (228). These forms of sensitivity analysis are interchangeably called DSA. However, DSA is largely superseded by the use of PSA which tests a range of parameters simultaneously followed by the distribution of model parameters inputted (228). In Appendix 5-7, it explains how to perform PSA using R as an integral part of uncertainty analysis of cancer biomarkers for targeted therapies in addition to the detailed R code. In R, the model can be run by the function defined by the modeler (R is known to be extremely flexible in this regard) and I define all parameters in the function of

psa.model.run. DSA modeling is similar to that of PSA; refer to supplementary R code for DSA simulation (Appendix 5-7).

In addition to this parameter uncertainty, an analysis of structural uncertainty can be performed by adapting this core model. For example, the structure of health states can be readily altered considering the natural course of disease progression of interest for local adaptation. Currently, three health states (PFS, PD, Dead) were designed as a default structure. The number of health states can be added or reduced. Example PSA output generated by this worked example is provided in Appendix 5-6.

DISCUSSION

This paper has introduced a core model which can be adaptable for the user's analysis to her or his specific datasets and requirements in assessing the value of cancer biomarkers. This guide demonstrated the model structure of strategy comparisons and data requirements relevant to the characteristics of cancer biomarker testing that require to be incorporated in the health economic modeling of cancer biomarkers for targeted therapies.

This paper has also provided a step-by-step guide to carrying out cost-effectiveness analysis for biomarker-guided therapies in the state-transition modeling framework and has provided R codes in vectoring data inputs, running the simulations, performing survival analysis, calculating base-case mean life years/QALYs, and performing sensitivity analyses. The user can adapt this core model to develop their own local model applied to his or her specific cancer biomarker testing technology and specific jurisdiction of reimbursement decision-making. Or, test developers can assess the potential value for money of their candidate cancer biomarker tests at an early stage of development by incorporating the

pertinent model inputs with necessary adaptations and modifications to this core model. For example, the user can adapt the structure of health states, the strategy arms to be compared against one another, transition probabilities, biomarker specific characteristics, cost and utility values, etc. However, for those who need to reconstruct time-to-event data from published Kaplan-Meier survival curve as part of building health economic models in R, there are two useful tutorial papers providing algorithms for the user to use (229, 230).

There are a couple of limitations that readers might wish to take into consideration when adapting this model for their local ones. First, this core model is constructed based on a state transition model and therefore, for those wishing to build a partitioned survival model (PSM) might require more time to adapt. However, PSM does not require many of modeling techniques as does with the state-transition model. Second, the user is required to have some understanding on the concepts of economic evaluations and HTA as well as programing in R. Therefore, there is still a programing language barrier for test developers to adapt or apply this core model to their data and requirements if the user (e.g. laboratory scientists) is not familiar with cost-effectiveness analysis and R coding. It requires some intermediate level of R programing/coding and conceptual understanding of economic evaluations of health technologies. Third, guiding on how to validate a model was not covered by this guide because this study intends to provide a step-by-step guide on how to build a model of co-dependent technologies rather than providing a guide to the validation of a specific model. Furthermore, this core model is built using 'exemplary' data inputs (not real dataset) and thus, as Eddy et al guided on the model validation(231), the concept of validity should apply to particular applications not to the model itself. Therefore, modelers wishing to adapt this core model to their local settings with specific dataset (e.g. 'real' data inputs from clinical trials) and assumptions applied to their specific decision problems, the process of model validation should be accompanied in their local adaptation

model. There are several guidance and checklist published on good practices of model validation (231-233).

A couple of areas can be recommended for further development to this core model. First, although the R codes provided in this guide are verified by running the model in R, it was not tested, to what extent, this model can be applicable to actual datasets. By applying this core model to published economic evaluations of biomarker-guided therapies, the generalizability of this model can be further validated. By doing so, it might give more insights on what circumstances this core model is adaptable, difficult to adapt or unadaptable at all. Second, this core model can be further developed to make it easily accessible for those unfamiliar with R. For example, it can be further developed to user-friendly interface web-based apps using Shiny R package as done by Strong et.al in assessing the value of information (234).

6. DISCUSSION

6.1. Research objective

Overall, this thesis sought to explore good practice in economic evaluations (EEs) of cancer biomarkers for targeted therapies and to provide a practical guide to conducting the cost-effectiveness analysis of companion cancer biomarkers. It reviewed modeling approaches and biomarker characteristics considered in previous model-based economic evaluations and conducted a cost-effectiveness analysis of a novel biomarker (HSP27 expression); these studies contributed to the development of a practical guide with a worked example of core model.

First, it aimed to explore how the use of biomarkers affects the cost-effectiveness of the corresponding therapies in oncology. Whether or not the integration of biomarker tests improved the cost-effectiveness of the corresponding targeted therapies. (First objective/Chapter 2)

Second, it aimed to highlight the current challenges and issues to be overcome to reach a consensus on methods and data requirements for EEs of cancer biomarkers. It investigated current practice of modeling and incorporating the characteristics of companion biomarkers when assessing the cost-effectiveness of biomarker-guided therapies. (Second objective/Chapter 3)

Third, it aimed to apply the study findings to assessment of the cost-effectiveness of an actual novel biomarker (HSP27 expression) as part of the EEs of corresponding targeted therapy (bevacizumab). The economic model of HSP27 expression was constructed based on what I found in previous literature review studies. (Third objective/Chapter 4)

Fourth, it aimed to provide a practical guide on how to model companion biomarkers when assessing the cost-effectiveness of co-dependent targeted therapies. I developed a core model with worked examples for readers to adapt. (Fourth objective/Chapter 5)

6.2. Key findings

The first objective of this thesis was to explore the impact of companion cancer biomarkers on cost-effectiveness of co-dependent targeted therapies; whether the use of biomarker tests makes targeted therapies cost-effective or not. The aim was to synthesise and critically appraise the cost-effectiveness findings and identify key factors driving the cost-effectiveness of biomarker-guided therapies. This study found that the inclusion of

companion biomarkers improved the cost-effectiveness of co-dependent targeted therapies; however, the improvement did not necessarily make targeted therapies cost-effective. Although the use of companion biomarkers saved some costs by stratifying patient groups responsive and unresponsive to the associated drugs, it appeared that the saving was not large enough to make targeted therapies cost-effective. Given the indirect influence of companion biomarkers, the cost-effectiveness of biomarker-guided therapies seemed to be driven by the characteristics of corresponding drugs rather than those of companion cancer biomarkers. Especially, high costing drugs continue to struggle to be cost-effective despite the integration of companion biomarkers in a cost-effectiveness analysis of co-dependent targeted therapies.

The second objective of this thesis was to review the current practice of modeling approaches and biomarker characteristics considered in EEs. This study found that there were no consistent modeling methods in assessing the value for money of biomarker-guided therapies. As an example, the comparative structure of applying strategy arms in EEs of companion biomarkers were so varied that it may lead to a different or even conflicting conclusion in terms of cost-effectiveness of biomarker-guided therapies. I reviewed EEs focusing on ten methods areas deemed to be specific issues and challenges faced by test developers when generating evidence of the health economic impact of biomarker tests. I found that many studies were not relevant because they conducted EEs of companion cancer biomarkers for targeted therapies in specific groups of patients with known biomarker status.

Among the studies included in the review (Chapter 3), all studies included the costs of biomarker testing. The most frequently ignored areas were preference-based outcomes, clinical utility, resource use and the timing of the relevant biomarker test. Only a handful

of studies considered the prevalence of a biomarker and unknown test result was also ignored. Furthermore, a significant challenge was observed in integrating patient preference values in EEs of biomarker-guided therapies given the indirect impact of cancer biomarkers on patient outcomes. Also, no studies explicitly considered the clinical utility of cancer biomarkers in their EEs. It is practically very difficult to generate the evidence of clinical value of cancer biomarkers especially when the biomarker is developed independently from the corresponding drug because of the indirect impact of biomarkers on clinical effectiveness of targeted therapies.

The third objective of this thesis was to conduct the cost-effectiveness analysis of a novel biomarker and assess whether the use of a biomarker test makes the targeted therapy cost-effective or not. This analysis also aimed to apply the previous findings from Chapters 2-3 in the health economic assessment of this novel biomarker, HSP27 expression. This study showed that the cost-effectiveness of testing HSP27 expression prior to the administration of bevacizumab produced conflicting results depending on the comparator strategy used in the analysis, which is in line with findings from previous literature reviews. When the intervention strategy was compared against the standard of care without testing, it was cost-effective. However, when it was compared against the new therapy without biomarker testing, it was not cost-effective. This indicates that HSP27 expression is not cost-effective as a predictive companion biomarker for bevacizumab in treating patients with metastatic melanoma. This may not necessarily mean that HSP27 expression is a bad biomarker for bevacizumab, but rather bevacizumab is in any case much better than dacarbazine in treating patients with metastatic melanoma independent of HSP27 expression.

The fourth objective of this thesis was to provide a practical guide to the methods of modeling companion biomarkers for targeted therapies in cancer. It showed solutions to resolve the modeling challenges and specific issues faced by test developers when assessing the cost-effectiveness of cancer biomarkers. This practical guide provided a step-by-step guide along with a core model for test developers to adapt for local requirements. This core model reflected the findings from previous literature reviews. For example, the previous literature review studies (Chapters 2 and 3) on modeling approaches of companion cancer biomarkers suggested some solutions to constructing the comparative analysis by employing the strategy of 'treat-all with standard care' as a baseline comparator arm rather than using the 'treat-all with new therapy'. The entire patient population should be considered including biomarker positive, negative and even unknown patient groups rather than only focusing on a pre-selected group of patients with a specific confirmed biomarker status. Furthermore, model inputs relevant to cancer biomarker testing should be all captured and incorporated in EEs of biomarker-guided therapies. Based on the previous findings, a worked example of core model was developed with step-by-step guide for test developers to use.

6.3. Study limitations

There are of course some limitations that I would like my audience to take into consideration when interpreting the findings of my studies and adapting my core model developed as part of my PhD thesis. First, the literature review of current practice in economic evaluations of companion cancer biomarkers (Chapter 3) was restricted to papers published in the last 5 years and thus may have excluded some relevant papers.

However, given that it aimed to review current practice of EEs in terms of modeling methods and data requirements, 5 years considered to be long enough to capture all recent EEs of companion biomarkers for targeted cancer biomarkers. Furthermore, 5 years was chosen in order to exclude any out-of-date approaches not applicable to current practice.

Second, the systematic literature review to see whether or not the use of companion biomarkers improves the cost-effectiveness of the corresponding targeted therapies (Chapter 2) was conducted for biomarker-guided therapies in metastatic colorectal cancer. It did not encompass all biomarker-guided therapies in cancer for the practical reason of conducting the study within the limited time of my PhD research. Therefore, the findings from this review might not necessarily be applicable to other cancer areas of biomarker-guided therapies. For example, if the cancer drug costs are reasonably priced from the time of reimbursement and market access, the cost-effectiveness of biomarker-guided therapies would not be necessarily driven by the high drug cost.

Third, the cost-effectiveness analysis of HSP27 expression prior to the administration of bevacizumab (Chapter 4) was conducted in order to explore the applicability of the findings from the two literature reviews on an actual candidate biomarker on top of the aiming to inform the cost-effectiveness of HSP27 expression testing. However, this analysis was challenged by the robustness of early stage clinical evidence. For example, the clinical data used in the analysis were based in a small-sized phase II single arm study and no head-to-head trial existed generated from a large-scale phase III randomized clinical study. However, this study assisted in informing me of practical challenges and issues faced by test developers who would mostly experience similar challenges with candidate biomarkers under development, and who would need to plan the evidence generation at

the early stage of technology development process so that their candidate biomarker tests can have better chance to be ensured of reimbursement and coverage by payers.

Fourth, although the core model and the step-by-step guidance (Chapter 5) were developed in order to ease the process of developing a health economic model for cancer biomarkers for test developers who may not necessarily health economic modelers. However, it still requires a certain level of understanding in EEs of health technologies and the basic concepts of economic modeling in order for the user to follow the guide together with the operation of core model. Furthermore, the user is required to have at least intermediate level of R coding to adapt this core model to local models to their needs using their own data and following local HTA requirements. Given R is a script-based programming language, the user needs to be able to understand the R scripts. However, this limitation can be resolved by further developing this core model to user-friendly web-based interface apps for example, using Shiny R.

6.4. Policy implications and evaluation recommendations

The thesis findings provide some policy implications and recommendations in assessing the value for money of companion biomarkers for targeted cancer therapies in the light of making reimbursement decisions of health technology assessment.

- The results suggest that there is no consistency and/or consensus when it comes to the modeling approaches in the health economic assessment of cancer biomarkers as part of the evaluation of corresponding therapies. It is recommended to fully capture the clinical and economic value of biomarker testing along the entire treatment pathway involved with biomarker testing.

- My literature review shows that cost-effectiveness analysis can produce conflicting results depending on the modeling approaches taken in the health economic assessments of biomarkers. For example, the review of mCRC therapies found that the use of different comparator arms led to conflicting cost-effectiveness results for the corresponding therapies. Therefore, it is recommended to reach a consensus on modeling methods and data requirements in assessing the value for money of companion biomarker tests as an integral part of that of co-dependent targeted therapies.
- My cost-effectiveness analysis of HSP27 expression suggests that testing HSP27 expression prior to the administration of bevacizumab in treating patients with metastatic melanoma is not cost-effective. It has saved some costs and contributed to improving the cost-effectiveness of bevacizumab, however, the saving was not sufficient to make a targeted bevacizumab strategy cost-effective. Furthermore, the EVPI analysis suggests further research costs cannot be justified to generate more evidence for assessing the test-treat strategy against the treat-all with dacarbazine; however some health gains might be possible by reducing the uncertainties around the comparative analysis of test-treat strategy against the treat-all with bevacizumab. Yet, the upper bound of research costs generated by EVPI analysis was too low for the Norwegian setting.
- Given the nature of indirect impact of companion biomarkers on the clinical effectiveness and cost-effectiveness of biomarker-guided therapies, test developers face challenges in generating evidence for reimbursement decisions. Some clarity on methods and evidentiary standards of health economic assessments of biomarkers need to be addressed by decision makers. A consensus

on evidentiary requirements for incorporating the characteristics of companion biomarkers need to be established and guided.

- National reference cost database for laboratory tests including companion biomarker tests needs to be established. The price of medical devices including biomarker testing kits/diagnostics is often set by negotiations between test developers and hospitals or set freely by individual laboratories. Therefore, it is likely to exist large variations in costing biomarker tests in EEs of biomarker-guided therapies even within the same jurisdiction. Furthermore, biomarker-guided therapies would require EEs to include a much wider range of cost items and more frequently than that of non-guided therapies; for example, capital costs or upfront infrastructure costs related to biomarker testing. Reimbursement decision makers need to clearly guide test developers on specific cost items to be included when assessing the value for money of companion biomarkers for targeted cancer therapies.

6.5. Contributions of this study to the field

The thesis contributes to the field of health economic assessments of companion biomarkers for targeted cancer therapies in several ways.

- First, it identifies current practice and describes inconsistent approaches to modeling companion biomarkers when evaluating the cost-effectiveness of biomarker-guided therapies in oncology.
- Second, it recommends possible solutions to the modeling approaches and data requirements for the health economic assessment of companion biomarkers for

targeted cancer therapies. The thesis findings can be a useful starting point to the development of methods guide in modeling companion biomarkers for co-dependent targeted therapies or in health technology assessment for biomarker-guided treatments.

- Third, it guides test developers or modelers wishing to assess the value for money of companion cancer biomarkers at an early stage of technology development. The core model provided in this thesis can be adapted by the user to their specific decision problem and specific data requirements.
- Fourth, it provides a step-by-step guide with example data and scenarios that have been developed based on the previous findings (Chapter 2-4). This thesis highlights good practice by constructing an economic model of companion cancer biomarkers which considers all biomarker-related parameters and scenarios.

6.6. Areas for further research adding to previous studies

A number of studies have previously addressed the challenges in evaluating co-dependent technologies, although some of these papers were not necessarily focusing on companion cancer biomarkers *per se*. While the scope of these studies is broader than that of my own work with respect to modeling the characteristics of companion biomarkers in economic evaluations of guided cancer therapies, some of their findings have raised similar issues.

Faulkner et al. (13) raised issues from payer and manufacturer perspectives. They identified five key areas to improve in evaluating personalised medicine. They suggested that health economic models should no longer compare a new medicine and an existing medicine but instead a 'test-and-treat' strategy and a 'treat-all' strategy. Also, they

suggested that the rate of false positives and false negatives, as well as their respective consequences, should be considered in the model. They then highlighted evidence gaps, such as whether the QALY is the best metric for personalised medicine, and clinical evidence when the diagnostic was developed as a stand-alone test rather than being co-developed with therapy. These aspects were similarly identified in my work however, my research suggested modeling three strategy arms instead of two, so that the 'test-treat' intervention strategy is compared with 'treat-all with existing care' and 'treat-all with new therapy' options.

Annemans et al. (122) presented ten methodological issues that arise when modeling personalised medicine. Similarly to my finding with respect to the current practice of modeling the characteristics of companion biomarkers, their paper also discussed the importance of capturing the clinical utility of the test. They argued that it is vital to evaluate the added value of a companion diagnostic test to its co-dependent therapy. They note that the correct reporting of sensitivity and specificity is a key element in modelling companion diagnostics however, information for patients with false negative and false positive test results is often lacking, which is in line with Faulker et al (13). In addition, combined use of different tests can lead to more complex models, which potentially causes a higher degree of uncertainty in the assessment. Also, as with my study, data gaps were found especially for key epidemiological data such as the prevalence of the biomarker or mutation in the population. They suggested performing early population-level simulations which can aid the identification and collection of critical data inputs. This early economic modeling can inform the manufacturer 'go' or 'no-go' or research priority setting decisions for co-dependent technologies such as companion biomarkers for targeted therapies in cancer. My tutorial paper in health economic modeling for companion biomarkers can be

useful as a step-by-step guide for the test developers and manufactures to adapt for their specific decision problems and country-specific settings.

Several studies performed systematic literature reviews to identify and analyse current methodological characteristics and approaches in evaluating genetic testing technologies.

First, Assasi et al.(235) systematically reviewed HTA reports on genetic tests. The study scope investigated in this review was broader than my own research. They included diagnostic, preventive genetic tests, prognostic, predictive or genetic tests guiding treatment. Only three of the fifteen studies identified involved predictive testing of the response to treatment. However, similar methodological challenges were found in this review such as adopting a third-party payer perspective (rather than a social perspective) or failing to capture the full range of outcomes and costs of testing technologies. However, since this review included diagnostic and preventive screening, the need to consider long-term psychological and social impacts were more pronounced in this study than mine and accordingly, more comprehensive frameworks were suggested for the evaluation of genetic testing technologies.

Second, Shabaruddin et al.(6) identified six existing systematic reviews of economic evaluations of genetics-and genomics-targeted technologies as examples of personalised medicine. They discussed existing challenges and summarised the data requirements of health economic assessments of pharmacogenetic technologies. The key data required were clinical effectiveness and utility, changes in health status, and resource use and associated costs, and the uptake of the test. Regarding issues specific to companion diagnostics, this study suggested that evidence that the testing improves patient outcomes is needed. However, generating the evidence for improved health outcomes is not always straightforward. If the companion biomarker tests were integrated into the clinical trials

of their co-dependent therapeutic agents, it can be assumed that their clinical utility is already reflected in the clinical evidence for the corresponding therapies. Otherwise, it is difficult to show the clinical utility of companion biomarkers in clinical practice given that the patient outcome of the combined test-therapy intervention is expressed in the clinical outcome of therapy. In other words, the clinical utility of companion biomarker tests is indirectly expressed in the patient outcome of their co-dependent therapies. Therefore, the clinical value of companion biomarker tests is often limited to the testing accuracy (clinical validity expressed in sensitivity and specificity) as I found in my research work.

Oosterhoff et al. (147) also conducted a systematic review on recent economic evaluations of diagnostic biomarkers and examined whether these studies dealt with specific issues related to the characteristics of diagnostic biomarkers. This review suggested that the incorporation on non-health outcomes and patient preferences is crucial to fully capture the potential value of diagnostic biomarkers. However, this study covered a wide range of biomarker tests including diagnosing, staging diseases, and guiding treatment. Despite the broad scope of their search, the number of papers identified appears to be low. Interestingly, this review suggested incorporating personal utility assessed by non-health outcomes, for example, the utility of diagnostic information ('value of knowledge') in genetic testing of relatives, or the discomfort experienced by patients while undergoing the test (process utility). It appears that genetic testing technologies require a broader definition of health utility, such as potential benefits to family members and relatives, knowledge to be informed of heritable disease, or preventive treatment decision-making. However, Buchanan et al. (236) found that non-health outcomes have limited applicability as standard outcome measures to be considered in economic evaluations, and alternative metrics such as personal utility are under-developed. Overall, the quality of effectiveness

data was weak, posing challenges to incorporating them in standard economic analyses. The authors continued with a similar argument about measuring the outcomes of genomic sequencing technologies in their recent publication (237). Similar to my research, they also raised the issue that the metrics currently recommended by HTA agencies (e.g. EQ-5D instrument) may not capture patient health outcomes, such as patient wellbeing before and after undergoing genomic sequencing technologies. Although the study scope of testing technologies investigated in this review was broader than my work, it also highlighted that the issue of not being able to capture the added value of testing needs to be further studied and a consensus needs to be reached in the field of health economics and HTA agencies. Husereau et al. (238) reviewed current Canadian approaches in evaluating personalised medicine, employing the methods of literature review and informal interviews with ten experts. They identified specific issues using the framework of the Canadian evaluation guideline and discussed some solutions to the issues identified. Their solutions include improving guidance on accurate valuation of testing costs (fixed, variable and other costs), defining interventions/comparators aligned with the rapid evolution of clinical pathways (e.g. test sequences combined with treatment may lead to multiple strategies), and further research on population preference heterogeneity and standards for disutility from harm. This study also suggested improving current guidelines for the economic evaluation of personalised medicine interventions in Canada. The expert interviews reached a consensus that a new paradigm will not be required but that personalised medicine requires more complex analyses. Similarly, Rogowski et al. (239) found that the principles and methods of current economic evaluations are appropriate for personalised medicine especially in oncology. However, some methods are under-developed or under-utilised (236, 237). The lack of specific guidance on the methods for

assessing the health economic value of co-dependent technologies identified in this thesis has also been identified by other studies (13, 122).

Adding to these previous studies, the studies presented in this thesis expand our understanding and knowledge of current practices and of the challenges faced by test developers in conducting economic evaluations of companion biomarkers for targeted cancer therapies in terms of modeling methods and data requirements. However, further efforts are required to make a consensus in the field of health economics, especially regarding how to measure and appraise preference-based utilities for biomarker testing. Further research is required to capture the full value of biomarkers particularly given the indirect impact of companion biomarker tests on patient benefits.

First, the current metrics for the measurement and valuation of health outcomes do not necessarily allow capturing the full value of patient preferences of companion biomarkers given their indirect impact on patient benefits. Further research is required to develop the methods on how to capture the full spectrum of patient benefits derived from biomarker tests and measure them appropriately.

Second, building on the findings of this thesis, further research is required to reach a consensus among experts and stakeholders including payers and patients with regard to best practice when evaluating the value for money of companion cancer biomarkers. We can then develop a methods guide on modeling approaches and data requirements when modeling companion biomarkers as part of economic evaluations of co-dependent targeted therapies based on the consensus reached among stakeholders. Furthermore, there is the issue of how to deal with biomarkers that are not cost-effective at even a zero price since their value for money is assessed in combination with co-dependent targeted therapies.

Third, it is required to revisit the current practice of HTAs of diagnostics/devices and pharmaceutical drugs which are currently being implemented in isolation from each other in many countries. With the advent of co-dependent health technologies such as biomarker-guided therapies, it gives rise to the need of integrating the HTA methods and procedures of the devices and the drugs rather than implementing them in isolation.

Fourth, an urgent area of further research concerns the evidence generation of clinical outcomes or clinical utility of biomarker tests. Currently, the clinical evidence on biomarker testing is limited to the performance accuracy (e.g. sensitivity and specificity). There is no consensus on the good practice for measuring and generating the clinical effectiveness of biomarker tests. For example, an enrichment trial design could be one of the potential solutions to this challenge however, this study design has limitations in generating clinical evidence for biomarker negative patients.

Lastly, from the practical point of view, extending my core model with an R package of Shiny would benefit decision-makers, health economists, or test developers who are not familiar with R coding. R Shiny would lower the barrier to using the core model even if users are not familiar with R coding.

In addition, beyond what I have done, there are other types of studies that can be built upon and further investigated for future research. First, systematic literature review is recommended to search all available methods guide on co-dependent technologies or test-guided therapies. I have provided two example guides (Australia and Scotland); however it would be clearer to find out if there are more methods guide researched by conducting a systematic review. It can then provide a comprehensive body of literature with all available methods guide for co-dependent technologies. It can then provide a solid ground for reviewers to compare what different approaches were taken and what data

requirements were addressed, etc. Second, built upon what found in the systematic review (as mentioned above), a consensus among stakeholders and experts can be pursued. I have also provided a framework of key items to be addressed in incorporating the characteristics of companion biomarker tests in economic evaluations of their corresponding test-guided therapies. Thus, a group consensus in methodological approaches and evidentiary standards for assessing the value for money of test-guided therapies can be made using consensus methods such as Delphi and nominal group (240). These studies can be performed built upon what I have reached and found. The studies done in my PhD and the systematic literature review on existing methods guide on co-dependent technologies can equip participants with the best available information and a structured environment for problem solving in reaching a consensus on methodological approaches and data requirements for health economic evaluations for companion biomarkers and test-guided therapies.

6.7. Conclusion

This thesis found that no consistency and consensus existed to the methods of existing economic evaluations of companion cancer biomarkers for targeted therapies. It was also shown that conflicting cost-effectiveness results were likely depending on what comparator arm was chosen and what comparison structure was designed in the model. My modelling study on a candidate companion biomarker test (HSP27 expression) for bevacizumab inferred the same; for example, the intervention strategy with new therapy (test-treat strategy) was cost-effective against treat-all with SOC however it was not cost-effective against treat-all with new therapy. Furthermore, this thesis highlighted good practice solutions to improve the current practices in incorporating companion biomarker

tests as an integral part of cost-effectiveness analysis of biomarker-guided targeted therapies. Also, a core model was developed and provided with worked examples and step-by-step tutorials, applying best practice solutions and modelling practicality acquired throughout the entire research phases in this thesis.

Based on the results of my PhD research, I want to see changes in the methods guide for the assessment of companion biomarkers for economic evaluation of targeted therapies in cancer. To be more specific, I would like to see the introduction of a methods guide for biomarker-guided therapies (e.g. companion biomarkers for targeted therapies) instead of applying different evaluation methods guide for drugs and diagnostics in isolation. As found in my research, there was inconsistency in incorporating the characteristics of companion biomarkers in the economic evaluation of targeted therapies and in structuring the comparative analysis between intervention and comparator arms. We need to reach a consensus on the methods of evaluating companion testing technologies as part of economic evaluations of their corresponding test-guided therapies. Built upon the consensus made, a methods guide for co-dependent technologies needs to be introduced, providing a coherent and unified guidance on good practices, reference case, evidentiary standards and data requirements for modelling the characteristics of companion biomarker tests.

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8. APPENDICES

APPENDIX 2-1 : SEARCH TERMS

(SEARCHED JUNE 25, 2018)

Database: EMBASE via Ovid

1	exp biological marker/
2	biomark*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
3	(molecul* mark* or tumo?r mark* or biologic* mark* or signature molecule*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
4	(cetuximab or Erbitux* or panitumumab or Vectibix* or bevacizumab or avastin* or aflibercept or ziv-aflibercept or zaltrap* or regorafenib or stivarga* or ramucirumab or cyramza* or irinotecan or campto*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
5	(target therap* or targeted therap* or personali#ed medicine* or companion diagnostic* or precision medicine* or codependent technolog*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
6	exp economic evaluation/
7	((cost* adj3 effective*) or (cost* adj3 benefit*) or (cost* adj3 utilit*) or willingness to pay or net benefit*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
8	(econom* adj3 evaluation*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
9	exp colon tumor/
10	1 or 2 or 3 or 4 or 5
11	6 or 7 or 8
12	9 and 10 and 11

Database: MEDLINE via Ovid

1	exp Biomarkers/
2	biomark*
3	molecul* mark* OR tumo?r* mark* OR biologic* mark* OR signature molecule*
4	exp Clinical Laboratory Techniques/
5	diagnos*
6	cetuximab or Erbitux* or panitumumab or Vectibix* or bevacizumab or avastin* or aflibercept or ziv-aflibercept or zaltrap* or regorafenib or stivarga* or ramucirumab or cyramza* or irinotecan or campto*

7	target therap* or targeted therap* or personali#ed medicine* or companion diagnostic* or precision medicine* or codependent technolog*
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	exp Cost-Benefit Analysis/
10	econom* adj3 evaluation*
11	(cost* adj3 effective*) or (cost* adj3 benefit*) or (cost* adj3 utilit*) or willingness to pay or net benefit*
12	9 or 10 or 11
13	exp Colorectal Neoplasms/
14	(colorectal or colon or colonic or bowel or rectum or rectal or intestin*) and (cancer* or tumo?r* or neoplasm* or carcinoma*)
15	13 or 14
16	8 and 12 and 15

Database: EconLit via Ovid

1	(biomark* or molecu* mark* or tumo?r mark* or biologic* mark* or signature molecule*).mp. [mp=heading words, abstract, title, country as subject]
2	(target therap* or targeted therap* or personali#ed medicine* or companion diagnostic* or precision medicine* or codependent technolog*).mp. [mp=heading words, abstract, title, country as subject]
3	((colorectal or colon or colonic or bowel or rectum or rectal or intestin*) and (cancer* or tumo?r* or neoplasm* or carcinoma*)).mp. [mp=heading words, abstract, title, country as subject]
4	1 or 2 or 3

Database: NHSEED

1	(biomarker*)
2	MeSH DESCRIPTOR Biomarkers EXPLODE ALL TREES IN NHSEED
3	MeSH DESCRIPTOR Clinical Laboratory Techniques EXPLODE ALL TREES IN NHSEED
4	(diagnos*) IN NHSEED
5	#1 OR #2 OR #3 OR #4
6	MeSH DESCRIPTOR Colorectal Neoplasms EXPLODE ALL TREES IN NHSEED
7	#5 AND #6

APPENDIX 2-2 : PICOS INCLUSION AND EXCLUSION CRITERIA

PICOS	Inclusion Criteria	Exclusion criteria
Population	Adult patients (≥ 16 years) treated with metastatic CRC	Patients < 16 years Diagnosed mild CRC No diagnosed CRC
Intervention	Cancer biomarkers for targeted therapies. Companion biomarkers licensed with corresponding targeted therapies	No diagnostic biomarker Universal screening tools Triage procedures Severity or progression analyses
Comparators	Targeted therapies with or without biomarkers	No comparative treatment Surgery
Outcomes	ICER, ICUR	Only costs or effectiveness
Study types	Economic evaluations (model or trial based CEA, CUA, CBA)	Cost-minimization analysis No economic evaluations. Published only as an abstract without reporting any outcomes. Publications reporting merely on methodological issues, reviews, comment letters and editorials. Abstracts reported elsewhere - this criterion should only be applied if the numerical values are the same in the full publication. NO English full-text.

APPENDIX 2-3 : OVERVIEW OF INCLUDED STUDIES

Study	Country	Perspective	Time horizon	Type of modeling	No. of strategies	Discount rate	Currency, price year	Funding	AB/ FT
Annemans 2007	Belgium	HCS	not reported	Trial-based model	3 strategies	NR	Euro, NR	NR	FT
Asseburg 2011	Germany	HCS	10-year	Patient-level simulation	2 strategies	5%	Euro, 2010	Commercial resource	FT
Behl 2012	USA	Payer	10 years	Markov model	4 strategies	3%	US\$, 2010	Public resource	FT
Blank 2011	Switzerland	HCS	Lifetime	Markov model	4 strategies	3%	Euro, NR	Academic resource	FT
Butzke 2016	Germany	HCS	Lifetime	Markov model	3 strategies	3%	Euro, 2013	Public resource	FT
Carlson 2010	USA	Payer perspective	NR	Unclear	3 strategies	NR	US\$, NR	NR	AB
Carvalho 2017	Brazil	Public healthcare system	Lifetime	Markov model	3 strategies	5%	US\$, 2016	Commercial resource	FT
Chaugule 2012	USA	Societal perspective	Lifetime	Markov model	2 strategies	3%	US\$, NR	NR	AB
Davari 2015	Iran	Iranian health care market	Unclear/Not reported	Unclear	6 strategies	NR	US\$, NR	NR	FT
Dos Santos 2015	Brazil	Brazilian private healthcare system	Lifetime	Markov model	2 strategies	5%	Brazil local currency, 2014	NR	AB
Ewara 2014	Canada Ontario	HCS	Lifetime	Markov model	3 strategies	5%	CA\$, 2012	Academic resource	FT
Gold 2009	USA	Medicare perspective	5-year	Decision tree	2 strategies	3%	US\$, 2007	Academic resource	FT

Graham 2014	France	French health collective perspective	Lifetime	semi-Markov model	2 strategies	4%	Euro, 2013	Commercial resource	FT
Graham 2016	USA	Third party payer	Lifetime	semi-Markov model	2 strategies	3%	US\$, 2014	Commercial resource	FT
Harty 2018	UK	UK NHS	10-year	Markov model	3 strategies	3.5%	GB£, NR	Commercial resource	FT
Hnoosh 2015 (AWMSG)	Wales, UK	NHS Wales	10-year horizon	Markov model	6 strategies	3.5%	GB£, NR	NR	AB
Hnoosh 2015 (NICE)	UK	NHS	10-year	Markov model	4 strategies	3.5%	GB£, NR	NR	AB
Hoyle 2013	UK NICE	HCS	10 years (lifetime)	Semi-Markov model	4 strategies	3.5%	GBP, 2011	Public resource	FT
Huxley 2017	UK	NHS NICE	30 years (lifetime)	Semi-Markov model	3 strategies	3.5%	GBP, 2015/16	Public resource	FT
Junqueira 2015 (Cmab)	Brazil	Public healthcare system	10 years	Markov model	2 strategies	5%	BRL, 2014	NR	AB
Junqueira 2015 (Cmab and Bmab)	Brazil	Public healthcare system	10 years	Markov model	2 strategies	5%	BRL, 2014	NR	AB
Kourlaba 2014	Greece	HCS	NR	Markov model	2 strategies	NR	Euro, 2014	NR	AB
Krol 2015	Netherlands, Belgium	Societal perspective (NL), Healthcare perspective (BL)	20-year horizon	Markov model	4 strategies	4% (NL), 3%(BL) for costs and 1.5% for effect	Euro, NR	NR	AB
Lawrence 2013	Canada	Healthcare system	Lifetime (to maximum of 10 years)	Markov model	4 strategies	5%	CA\$, 2011	Commercial resource	FT

Mittmann 2009	Canada	HCS	Duration of the clinical trial (18-19 months)	Trial-based model	2 strategies	Discounting not applied given the short time horizon	CA\$, 2007	No external funding	FT
Moreno 2012	Spain	not reported	not reported	Unclear	3 strategies	NR	Euro, NR	NR	AB
Niedersuess-Beke 2015	Austria	HCS	Not reported	Unclear	2 strategies	NR	Euro, 2013	NR	AB
Norum 2006	Norway	third party payer	Unclear	Decision tree	2 strategies	Not discounted because all benefits and costs occurred within a few months.	NOK, 2005	Public resource	FT
Obradovic 2008	USA	Healthcare payer	Lifetime	Decision tree	3 strategies	NR	US\$, 2006	Academic resource	FT
Ontario HTA 2010	Ontario, Canada	HCS	Lifetime	Markov model	7 strategies	5%	CA\$, 2009	Public resource	FT
Ortendahl 2014	USA	Not reported	Lifetime	Unclear	2 strategies	NR	US\$, 2013	NR	AB
Pichereau 2010	France	Hospital	Lifetime	Decision tree	2 strategies	NR	Euro, 2006	No financial support	FT
Riesco-Martinez 2016	Canada	Canadian public health care system	5-year	Markov model	3 strategies	5%	CA\$, 2012	Commercial resource	FT
Rivera 2017	Spain	National Health System	Lifetime (max 20 years assumed)	Semi-Markov model	2 strategies	3%	Euro, 2015	Commercial resource	FT
Saito 2017	Japan	Japanese healthcare payer	5-year	Markov model	3 strategies	2%	JPY, NR	NR	FT
Samyshkin 2011	UK	UK NHS	Lifetime	semi-Markov model	3 strategies	NR	GBP, NR	NR	AB

Shankaran 2015	USA	Payer perspective	2 years (trial period)	Decision tree	2 strategies	0%	US\$, 2013	Commercial resource	FT
Shiroiwa 2010	Japan	Healthcare payer	2.5 years	Markov model	3 strategies	3%	US\$, 2010	Commercial resource	FT
Souza 2017	Brazil	Public health system perspective	20 years	Markov model	2 strategies	5%	BRL, NR	Commercial resource	AB
Starling 2007	UK	NHS perspective	Lifetime	Trial-based model	2 strategies	3.5%	GB£, NR	Commercial resource	FT
Vargas-Valencia 2015	Columbia	Not reported	Lifetime	Markov model	2 strategies	5%	US\$, NR	Not reported	AB
Vijayaraghavan 2012	USA, Germany	HCS	Lifetime	Markov model	6 strategies	NR	US\$, 2009 Euro, 2009	Commercial resources	FT
Wen 2015	China	HCS	10 years (almost lifetime; all nearly dead)	Markov model	4 strategies	3%	US\$, 2014	No funding	FT
Wu 2017	China	Chinese medical insurance perspective	10 years	Markov model	3 strategies	5%	US\$, 2016	Public resource	FT
Xu 2016	USA	HCS (Medicare, Veteran)	3 years	Markov model	2 strategies	3%	US\$, 2015	NR	AB
Zhou 2016	China	Societal perspective (because travel fees and absenteeism fees constituted the indirect costs). However, the paper stated that it used Chinese HCS perspective	Lifetime	Markov model	Two analyses performed. Analysis 1: 4 strategies; Analysis 2: 4 strategies	3%	US\$, NR	No funding	FT

AB; abstract, FT; full text, HCS; healthcare system, NR; not reported.

APPENDIX 2-4 : COST-EFFECTIVENESS RESULTS OF ALL INCLUDED PAPERS

Study	Treatments/Strategies	Biomarker	Outcome measure	ICER (/LYs)	ICER (/QALYs)	Conclusion based on outcome
Annemans 2007	1. Cmam + Irinotecan (6-week rule, 12 week rule) 2. Current treatment	NS	LYs	1. Cmam + Irinotecan (6-week rule): £16766 2. Cmam + Irinotecan (12-week rule): £40273	-	Cmam + Irinotecan is cost-effective in Belgium
Asseburg 2011	1. Cmam + FOLFIRI 2. Bmam + FOLFOX	KRAS	LYs	Cmam+FOLFIRI: €15,020 compared to Bmam + FOLFOX	-	First line treatment with Cmam plus FOLFIRI offers a cost-effective treatment option versus Bmam plus FOLFOX for KRAS WT genotype pts in Germany. Thus, KRAS testing should be performed on all presenting cases of mCRC to ensure access to this treatment option.
Behl 2012	1. No Cmam 2. KRAS and BRAF testing + Cmam 3. KRAS testing + Cmam 4. Cmam without testing	KRAS, BRAF	LYs	KRAS and BRAF testing + Cmam: US\$648,396* KRAS testing + Cmam: US\$672,216* Cmam without testing: US\$827,913*	-	Screening for KRAS and BRAF improves the cost-effectiveness of Cmam. However, ICERs remain above the generally accepted threshold. Although we cannot confirm that Cmam is a cost-effective use of healthcare resources, we can confirm that KRAS testing is cost-saving.
Blank 2011	1. No test, no Cmam 2. KRAS/BRAF testing 3. KRAS testing 4. No test, Cmam all	KRAS, BRAF	QALYs	1. no test, no Cmam (reference strategy): dominated 2. KRAS/BRAF testing: euro 62,653 compared to the reference strategy	-	Testing for KRAS and BRAF mutations prior to Cmam treatment of chemofactory mCRC patients is clinically appropriate and economically favorable, despite high costs for predictive testing.

				3. KRAS testing: euro 313,537 compared KRAS/BRAF testing 4. No test, Cmam all: euro 314,588 compared to KRAS testing		
Butzke 2016	Strategy 1. dose reduction (WT receive standard dose of irinotecan, hetero-and homozygotes receive a dose reduction of irinotecan by 25%) Strategy 2. prophylactic administration of bone marrow proective GCSF growth factor analogs (all pts receive standard dose of irinotecan, hetero-and homozygotes additionally receive the growth factor 'pegfilgrastim') Strategy 3. no genetic test (all pts receive standard dose of irinotecan)	UGT1 A1	QALYs	-	Genetic test + irinotecan (dose reduction): dominant over two other strategies.	UGT1A1 testing and dose reduction is more effective, and cost-saving compared to the current standard of no-testing. UGT1A1 testing prior to irinotecan-based chemotherapy dominates non-personalized care in Germany.
Carlson 2010 (abstract)	1. Cmam alone 2. BSC 3. KRAS testing plus Cmam for KRAS WT pts and BSC for KRAS MT pts	KRAS	QALYs	Cmam for all : \$357,224 compared to BSC KRAS testing + Cmam : \$264,644	-	Use of KRAS testing to select pts for Cmam can reduce costs with a negligible impact on QALYs as compared to using Cmam for all pts. However, the CE of KRAS testing vs. BSC remains well above commonly used cost-effectiveness thresholds

Carvalho 2017	1. Pmab 2. Cmab 3. BSC	RAS	LYs	1. Pmab: US\$52772 2. Cmab: US\$58240	-	Both Pmab and Cmab are not cost-effective in patients with RAS WT mCRC
Chaugule 2012	1. Cmab + BSC 2. BSC alone	KRAS	QALYs	-	Cmab + BSC: US\$ 313,113 compared to BSC	Cmab is not cost-effective in KRAS WT pts with mCRC
Davari 2015	1. FOLFIRI, FOLFOX, CAPOX without the addition of Cmab 2. FOLFIRI, FOLFOX, CAPOX with the addition of Cmab	KRAS	LYs, QALYs	1. FOLFIRI vs. FOLFIRI+Cmab \$654846 2. FOLFOX vs. FOLFOX+Cmab \$458113 3. CAPOX vs. CAPOX+Cmab \$461989	1. FOLFIRI vs. FOLFIRI+Cmab \$859756 2. FOLFOX vs. FOLFOX+Cmab \$1588143 3. CAPOX vs. CAPOX+Cmab \$1567786	Addition of Cmab to FOLFIRI, FOLFOX, CAPOX (Capecitabin+oxaliplati) is not cost effective
Dos Santos 2015 (Abstract)	1. Pmab + mFOLFOX6 2. Bmab + mFOLFOX6	RAS	LYs, QALYs	1. Pmab + mFOLFOX6 vs. Bmab + mFOLFOX6 : 25,798 BRL per LYs gained	1. Pmab + mFOLFOX6 vs. Bmab + mFOLFOX6 : 34,960 BRL per QALYs gained	Pmab is clearly cost-effective compared to Bmab for treatment of wild-type RAS mCRC in Brazil.
Ewara 2014	1. Bmab + FOLFIRI 2. Cmab + FOLFIRI 3. Pmab + FOLFIRI	KRAS	QALYs	-	1. Bmab + FOLFIRI : Dominant 2. Cmab + FOLFIRI : Dominated 3. Pmab + FOLFIRI : Dominated	Bmab+FOLFIRI is cost-effective. Bmab + FOLFIRI found to be dominant over the other two strategies. The other two strategies are dominated by Bmab + FOLFIRI. However, sensitivitiy analysis showed that Cmab + FOLFIRI is being cost-effective under certain range of parameter values - thus, further investigation needed for Cmab.
Gold 2009	1. Usual care: all pts receive a standard intermediate dose of irinotecan. 2. Genetic testing strategy: test + Irinotecan	UGT1A1	QALYs	-	Genetic testing + Irinotecan : Dominant compared to no testing strategy	Pharmacogenetic testing for UGT1A1*28 variant homozygosity may be cost-effective, but only if irinotecan dose reduction in homozygotes does not reduce efficacy. Future studies to evaluate reduced-dose

						efficacy in homozygotes should be considered.
Graham 2014	1. Pmab 2. Bmab	KRAS, RAS	LYs, QALYs	Pmab : €26,918	Pmab : €36,577	Pmab plus mFOLFOX represents good value for money compared to a current SOC Bmab plus mFOLFOX6
Graham 2016	1. Panitumumab in pts with KRAS WT status 2. Cetuximab in pts with KRAS WT status	KRAS	LYs, QALYs	Dominant (panitumumab dominates) -\$307,432	Dominant (panitumumab dominates) -\$648,345	Compared to Cmab, the study suggested that Pmab is favorable.
Harty 2018	1. Cmab+FOLFIRI 2. FOLFIRI	KRAS, RAS	QALYs	-	3 cohorts compared ITT (intention-to-treat) group: £130,929 KRAS WT group: £72,053 RAS WT group: £44,185	RAS WT group showed the lowest ICER and thus, it is the most cost-effective of the three groups
Hnoosh 2015 (AWMSG) (Abstract)	1. Cmab + either FOLFOX, FOLFIRI, CAPOX 2. FOLFOX 3. FOLFIRI 4. CAPOX	RAS	QALYs	-	Cmab + FOLFOX £29,512 compared to FOLFOX alone. Cmab + FOLFIRI £35,731 compared to FOLFIRI alone.	Cmab is cost-effective and a good use of NHS Wales resource through stratification of RAS wild-type patients
Hnoosh 2015 (NICE) (Abstract)	1. Cmab + either FOLFOX, FOLFIRI, CAPOX 2. FOLFOX 3. FOLFIRI	RAS	QALYs	-	Cmab+FOLFOX: £46503 compared to FOLFOX alone Cmab+FOLFIRI: £55971 compared to FOLFIRI alone	Cost-effectiveness of Cmab could be deemed favorable when considering it as end-of-life medicine
Hoyle 2013	1. Cmab 2. Cmab + Irinotecan 3. Pmab 4. BSC	KRAS	LYs, QALYs	1. Cmab £72,000 compared to BSC 2. Cmab + Irinotecan £64,000 compared to BSC	1. Cmab £95,000 compared to BSC 2. Cmab + Irinotecan £88,000 compared to BSC	All three strategies (Cmab, Cmab+Irinotecan, Pmab) are not cost-effective.

				3. Pmab £153,000 compared to BSC	3. Pmab £187,000 compared to BSC	
Huxley 2017	1. FOLFOX (reference strategy) 2. Cmab + FOLFOX 3. Pmab + FOLFOX	RAS	QALYs	-	Cmab+FOLFOX vs. FOLFOX : £104205 per QALYs gained Pmab + FOLFOX vs. FOLFOX : £204103 per QALY gained	Cmab and Pmab in combination with chemotherapy are likely to be poor value for money
Junqueira 2015 (RAS subgroup) (Abstract)	1. Cmab + FOLFIRI 2. FOLFIRI	RAS	LYs	BRL 66090.91	-	Cmab+FOLFIRI is cost-effective for a subgroup of patients with RAS wild-type
Junqueira 2015 (Cmab and Bmab) (Abstract)	1.Cmab+FOLFIRI 2.Bmab+FOLFIRI	RAS	LYs	Cmab+FOLFIRI: dominant, cost-saving	-	The use of Cmab shown significant and meaningful benefits while being cost-saving to HCS in Brazil.
Kourlaba 2014 (Abstract)	1. Pmab + FOLFOX6 2. Bmab + FOLFOX6	RAS	QALYs	-	1. Pmab + FOLFOX6 : €34,644 compared to Bmab + FOLFOX6	Pmab + mFOLFOX6 is cost-effective.
Krol 2015 (Abstract)	1. Cmab + FOLFIRI 2. FOLFIRI 3. Cmab + FOLFOX 4. FOLFOX	RAS	QALYs	-	1. 86180euro (NL) and €55430(BL) for Cmab + FOLFIRI vs. FOLFIRI	ICUR results were close to CET. ICURs strongly differed from NL and BL. It is mainly due to lower drug costs in BL.
Lawrence 2013	1. FBC 2. Bmab + FBC 3. Cmab + FBC 4. Pmab + FBC	KRAS	QALYs	-	FBC - Bmab + FBC : CA\$131,600 Pmab + FBC : Dominated Cmab + FBC : CA\$3,844,571	Bmab + FBC offers the best value for money in KRAS wt patient population.

Mittmann 2009	1. Cmam + BSC 2. BSC	KRAS	LYs, QALYs	1. For unselected mCRC pts, Cmam+BSC: CA\$199,742 compared to BSC. 2. For KRAS WT pts, Cmam + BSC: CA\$120,061 compared to BSC.	1. For unselected mCRC pts, Cmam + BSC : CA\$299,613 compared to BSC. 2. For KRAS WT pts, Cmam+BSC: CA\$186,761 compared to BSC.	ICER of Cmam over BSC alone for unselected mCRC pts was high and sensitive to drug costs. ICER was lower when the analysis was limited to pts with KRAS WT.
Moreno 2012 (Abstract)	1. Scenario A: KRAS WT pts receive weekly Cmam + FOLFOX 2. Scenario B. Pmam + FOLFOX 3. Scenario C. Cmam biweekly + FOLFOX	KRAS	Response rate	Scenario A vs. B : €4394 Scenario C vs. B : €4432	-	1st line oxaplatin combinations of biweekly Cmam for WT and Bmam for MT optimise cost per additional response rate rather than Pmam-based schedules
Niedersue ss-Beke 2015	1.Predictive biomarker testing 2.No predictive biomarker testing	KRAS, RAS, future bioma rker	Lys	€26.276 (KRAS testing scenario) €9.686 (RAS testing scenario) €3.948 (future but achievable biomarker scenario)	-	Testing predictive biomarkers is cost-saving in mCRC
Norum 2006	1. 3rd line chemotherapy (Cmam + Irinotecan) 2. No 3rd line chemotherapy	EGFR	LYs	The range of ICERs was between €205,536 and €323,040	-	Cmam + Irinotecan as 3rd line therapy in mCRC is promising, but a very expensive antibody. Reduced drug cost and/or improved overall survival may alter this conclusion
Obradovic 2008	1. No UGT1A1 genotyping + SOC 2. UGT1A1 testing + Reduced initial irinotecan dose (20% reduction) 3. UGT1A1 testing + standard irinotecan dose+ Prophylactic use of GCSF	UGT1 A1	Severe neutropenia occurrence (severe neutropenia prevention) , LYs	1. Genotyping + reduced initial irinotecan dose : (African group) : cost-saving compared to No genotyping strategy (Asian group) : US\$6,818,203 (Caucasian group) : cost-saving compared to No genotyping strategy	-	Genotyping in combination with reduced irinotecan dose for genotype pts was cost-saving for the population of African and Caucasian origin. By contrast, genotyping was not cost-effective for the population of Asian ancestry. The prophylactic use of GCSFs in genotype pts was not cost-effective for any population group.

				2. Genotyping + Prophylactic use of GCSF : (African group) : US\$3,506,260 (Asian group) : US\$7,371,770 (Caucasian group) : US\$3,836,998		
Ontario HTA 2010	0. BSC (no KRAS test; no treatment) 1a. KRAS testing + Cmab 1b. No KRAS testing + Cmab 2a. KRAS testing + Pmab 2b. No KRAS testing + Pmab 3a. KRAS testing + Cmab + Irinotecan 3b. No KRAS testing + Cmab + Irinotecan	KRAS	QALYs	-	0. BSC (no KRAS test; no treatment) 1a. KRAS testing + Cmab : \$54,802 compared to BSC 1b. No KRAS testing + Cmab : Dominated compared to BSC 0. BSC (no KRAS test; no treatment) 2a. KRAS testing + Pmab : \$47,795 compared to BSC 2b. No KRAS testing + Pmab : \$308,236 compared to BSC 0. BSC (no KRAS test; no treatment) 3a. KRAS testing + Cmab + Irinotecan : \$42,710 compared to BSC 3b. No KRAS testing + Cmab + Irinotecan : \$163,396 compared to BSC	All strategies considering KRAS testing found to be cost-effective compared to no-KRAS-testing strategies.
Ortendahl 2014	1. FOLFIRI + Cmab 2. FOLFIRI + Bmab	KRAS, RAS	LYs, QALYs	1. For KRAS WT pts, FOLFIRI + Cmab : US\$97297 compared to Bmab + FOLFIRI	1. For KRAS WT pts, FOLFIRI + Cmab : US\$122704 compared to Bmab + FOLFIRI	Cmab + FOLFIRI improve health outcomes and use financial resource more efficiently compared to Bmab + FOLFIRI

				2. For a subset of RAS WT pts, FOLFIRI + Cmab : US\$77380 compared to Bmab + FOLFIRI	2. For a subset of RAS WT pts, FOLFIRI + Cmab : US\$99,636 compared to Bmab + FOLFIRI	
Pichereau 2010	1. UGT1A1 genotyping + irinotecan therapy 2. No UGT1A1 genotyping + Irinotecan therapy	UGT1 A1	Number of neutropenia avoided	Genotyping strategy : €942.8 to €1090.1	-	UGT1A1 genotype screening before irinotecan treatment is a cost-effective strategy for the hospital.
Riesco-Martinez 2016	Strategy 1 (reference strategy: EGFRi monotherapy in 3rd line). 1st LINE : Bmab+FOLFIRI/FOLFOX (1st Line), 2nd LINE : FOLFIRI/FOLFOX, 3rd LINE : EGFRi Strategy 2 (EGFRi and Irinotecan in 3L). 1L : Bmab+FOLFIRI/FOLFOX, 2L : FOLFIRI/FOLFOX, 3L : EGFRi + irinotecan Strategy 3 (EGFRi in 1L). 1L : EGFRi + FOLFIRI/FOLFOX, 2L : Bmab + FOLFIRI/FOLFOX, 3L : best supportive care	KRAS, RAS	QALYs	-	Strategy 2 : \$119,623 compared to Strategy 1 Strategy 3 : \$3,176,591 compared to Strategy 1	1st line of EGFRi is not cost-effective at its current pricing relative to Bmab
Rivera 2017	1. Pmab + mFOLFOX6 2. Bmab + mFOLFOX6	RAS	LYs, QALYs	€16,567	€22,794	Pmab+mFOLFOX6 is more cost-effective than Bmab+mFOLFOX6 for the first line treatment of RAS wild-type mCRC
Saito 2017	No testing strategy: Anti-EGFR therapy without testing	RAS	LYs, QALYs	RAS screening: JYP2,574,111	RAS screening: JYP3,049,132	Comprehensive screening (comprehensive molecular profiling) is more cost-effective

	2. RAS screening : RAS mutation screening before anti-EGFR therapy 3. Comprehensive screening : comprehensive molecular profiling before anti-EGFR therapy using CancerPlex to screen for mutations that predict a poor response.			Comprehensive screening: JYP3,587,395	Comprehensive screening: JYP4,260,187	than RAS screening before administering anti-EGFR therapies
Samyshkin 2011	1. Bmab + Chemotherapy 2. Cmab + Chemotherapy 3. Pmab + Chemotherapy	KRAS	QALYs	-	Cmab+FOLFIRI : £30,665 compared to FOLFIRI alone. Bmab + FOLFOX : £17,626 compared to FOLFOX alone. Pmab + FOLFOX : £15,326 compared to FOLFOX alone.	Cmab plus FOLFIRI is the most cost-effective for pts with KRAS WT tumors. ICERs of Cmab + Chemotherapy (CT), Bmab + CT, and Pmab + CT are within the commonly accepted threshold of CE in UK
Shankaran 2015	1. FOLFIRI plus Cmab in treatment-naïve patients with KRAS wt type in mCRC 2. FOLFIRI plus Bmab treatment-naïve patients with KRAS wt type in mCRC	KRAS, RAS	LYs, QALYs	KRAS-WT patients: Cmab+FOLFIRI \$86,487 per LY RAS-WT patients: Cmab_FOLFIRI \$73,731 per LY	KRAS-WT patients: Cmab+FOLFIRI \$107,630 per QALY RAS-WT patients: Cmab+FOLFIRI \$93,785 per QALY	Results were more favorable for Cmab in RAS-WT patients
Shiroiwa 2010	1. KRAS testing + Cmab (WT - Cmab, MT - BSC) : Strategy A 2. No KRAS testing + all Cmab : Strategy B 3. No KRAS testing + all BSC : Strategy C	KRAS	LYs, QALYs	1. KRAS testing + Cmab : dominant compared to no KRAS testing 2. KRAS testing : US\$120,000 compared to no-Cmab strategy 3. No KRAS testing : US\$160,000 compared to no Cmab strategy	1. KRAS testing + Cmab : dominant compared to no KRAS testing 2. KRAS testing : US\$180,000 compared to no-Cmab strategy 3. No KRAS testing : US\$230,000 compared to no Cmab strategy	KRAS testing is dominant compared to no-KRAS testing strategy. However, ICER of Cmab + KRAS testing is US\$180,000 per QALYs compared to no-Cmab strategy.

Souza 2017	1. Cmam + Chemotherapy 2. Chemotherapy alone	RAS	LYs	R\$56,750	-	The addition of Cmam to the standard chemotherapy is cost-effective
Starling 2007	1. Cmam + Irinotecan 2. Active/best supportive care (ASC/BSC)	EGFR	LYs, QALYs	£42,975	£57,608	ICERs for Cmam+Irinotecan is relatively high compared to other healthcare interventions.
Vargas-Valencia 2015	1. Pmam + FOLFOX 2. Cmam + FOLFIRI	RAS	LYs	Pmam + FOLFOX US\$ 21,613.42 Cmam + FOLFIRI US\$ 23,036.94	-	Pmam showed treatment outcomes improvement vs. Cmam for wt RAS pts at a lower cost per life year.
Vijayaraghavan 2012	1. KRAS testing + Cmam 2. KRAS testing + Pmam 3. KRAS testing + Combination therapy (Cmam + Irinotecan) 4. No testing + Cmam 5. No testing + Pmam 6. No testing + Combination therapy (Cmam + Irinotecan)	KRAS	LYs	1. No testing + Pmam : higher cost same effectiveness compared to KRAS testing + Pmam 2. No testing + Cmam : higher cost same effectiveness compared to KRAS testing + Cmam 3. No testing + Combination therapy : higher cost same effectiveness compared to KRAS testing + Combination therapy	-	Using KRAS testing to limit use of EGFR inhibitors (Cmam/Pmam) to pts with KRAS WT results in net savings of \$7500 to \$12400 (for USA), while net savings of €3900 to €9600 (for Germany)
Wen 2015	1. Pts with KRAS testing treated with Cmam and FOLFIRI (KRAS-Cmam) 2. Pts with RAS testing treated with Cmam and FOLFIRI (RAS-Cmam) 3. Pts with KRAS testing treated with Bmam and FOLFIRI (KRAS-Bmam)	KRAS, RAS	Quality-adjusted life-months (QALMs)		1st and 2nd line KRAS-Bmam \$6,145.84 per QALMs RAS-Bmam \$6,201.34 per QALMs RAS-Cmam \$6,263.86 per QALMs KRAS-Cmam \$6,963.70 per QALMs	RAS screening prior to Cmam seems to be a cost-effective strategy in the time of monoclonal antibodies therapies. However, KRAS-Cmam strategy dominated by other 3 strategies. RAS-Bmam seems the most cost-effective strategy but the gained QALM was the shortest. Compared to other 3 strategies, RAS-Cmam achieved the highest gained QALM of 21.85

	4. Pts with RAS testing treated with Bmab and FOLFIRI (RAS-Bmab)					
Wu 2017	1. Cmab + FOLFIRI (with or without patient assistance programme) 2. FOLFIRI	RAS	LYs, QALYs	Cmab + FOLFIRI with PAP: \$12,107 Cmab + FOLFIRI without PAP: \$23,393	Cmab + FOLFIRI with PAP: \$14,049 Cmab + FOLFIRI without PAP: \$27,145	RAS testing with Cmab is cost-effective, when PAP is available, at a willingness to pay threshold of China (\$22,200/QALY)
Xu 2016	1.Pmab 2.Cmab	NR	LYs, QALYs	-	-	Pmab dominates over Cmab. Pmab has a cost advantage over Cmab
Zhou 2016	Analysis I: 1. KRAS-Cmab 2. KRAS-Bmab 3. RAS-Cmab 4. RAS-Bmab Analysis II: 1. FOLFOX-Cmab 2. FOLFOX-Bmab 3. FOLFIRI-Cmab 4. FOLFOX-Bmab	KRAS, RAS	Quality-adjusted life years (QALYs)	-	Analysis I (KRAS-wt vs. RAS-wt): 1. KRAS-Cmab (Dominated) \$88,394.09 2. KRAS-Bmab (Dominated) \$80,797.82 3. RAS-Cmab (420,700.50 compared to RAS-Bmab) \$82,590.72 4. RAS-Bmab (n.a) \$75.358.42 Analysis II (RAS wt): 1. FOLFOX-Cmab (Dominated) 2. FOLFOX-Bmab (Dominated) 3. FOLFIRI-Cmab (Dominated) 4. FOLFOX-Bmab (Undominated)	Analysis 1 : RAS wt testing is more cost-effective than KRAS wt testing before treatment. It is the first head to head cost-effectiveness study to evaluate predictive testing for extended RAS-wt in mCRC in the context of targeting Cmab/Bmab treatment. The results demonstrate that it was economically favorable to identify pts with extended RAS-wt status. Furthermore, FOLFIRI plus Bmab was the preferred strategy compared with other strategies in pts with extended RAS wt.

*Recalculated compared to No Cmab strategy

Bmab, bevacizumab; Cmab, Cetuximab; EGFR, epidermal growth factor receptor; ICER, incremental cost-effectiveness ratio; KRAS, kirsten rat sarcoma; RAS, rat sarcoma; LYs, life years; NS, not specified; NR, not reported; PAP, patient assistance program; Pmab, panitumumab; QALYs, quality adjusted life years; QALMs, quality adjusted life months; SOC, standard of care; WT, wild-type.

APPENDIX 2-5 : QHES SCORING PER STUDY

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Score
Annemans 2007	yes	yes	no	no	yes	yes	no	no	yes	yes	no	yes	no	no	no	no	48
Asseburg 2011	yes	yes	yes	n/a	yes	yes	no	yes	yes	no	no	yes	yes	no	yes	yes	75
Behl 2012	yes	no	yes	n/a	yes	yes	yes	yes	yes	no	no	yes	yes	no	yes	yes	76
Blank 2011	yes	yes	yes	n/a	yes	yes	no	yes	yes	yes	no	yes	yes	no	yes	yes	81
Butzke 2016	yes	yes	yes	n/a	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	99
Carvalho 2017	yes	yes	yes	no	yes	yes	no	yes	yes	yes	no	yes	yes	no	yes	yes	81
Davari 2015	yes	yes	yes	n/a	yes	yes	no	no	yes	no	no	no	no	no	yes	yes	53
Ewara 2014	yes	yes	yes	n/a	yes	yes	yes	yes	no	yes	no	yes	yes	yes	yes	yes	84
Gold 2009	yes	yes	no	n/a	yes	yes	no	yes	no	yes	no	yes	yes	no	yes	yes	65
Graham 2014	yes	yes	yes	n/a	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	no	yes	88
Graham 2016	yes	yes	yes	n/a	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	93
Harty 2018	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	no	yes	no	no	yes	yes	72
Hoyle 2013	yes	yes	yes	n/a	yes	yes	yes	yes	yes	yes	no	yes	yes	no	yes	yes	86
Huxley 2017	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	100
Lawrence 2013	yes	yes	yes	n/a	yes	yes	no	yes	yes	yes	no	yes	yes	no	no	yes	73
Mittmann 2009	yes	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	no	yes	no	yes	yes	79
Norum 2006	yes	yes	no	n/a	yes	yes	no	no	yes	no	no	yes	yes	yes	yes	yes	66
Obradovic 2008	yes	yes	no	yes	yes	yes	no	no	yes	yes	no	no	no	no	yes	yes	52
Ontario HTA 2010	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	no	91
Pichereau 2010	yes	yes	no	n/a	yes	yes	no	yes	no	yes	no	yes	yes	no	yes	yes	65

Riesco-Martinez 2016	yes	yes	no	n/a	yes	yes	yes	yes	yes	yes	no	yes	no	no	yes	yes	71
Rivera 2017	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes	93
Saito 2017	yes	yes	no	no	yes	yes	no	yes	yes	yes	no	yes	yes	no	yes	no	70
Shankaran 2015	yes	yes	yes	n/a	yes	yes	no	no	yes	no	no	yes	yes	no	yes	yes	68
Shiroiwa 2010	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes	no	yes	yes	87
Starling 2007	yes	yes	no	n/a	yes	yes	yes	yes	no	yes	yes	no	yes	no	yes	yes	69
Vijayaraghavan 2012	yes	yes	yes	n/a	yes	no	no	yes	no	yes	no	yes	yes	no	yes	yes	67
Wen 2015	yes	yes	no	n/a	yes	no	no	yes	no	no	no	yes	no	no	no	yes	38
Wu 2017	yes	yes	no	no	yes	Yes	no	yes	no	yes	no	yes	no	no	yes	yes	58
Zhou 2016	yes	yes	no	n/a	yes	Yes	no	yes	yes	no	no	yes	no	no	yes	yes	60

APPENDIX 3- 1 : SEARCH STRATEGY/SEARCH TERMS

Database: Medline

- 1 *Neoplasms/
- 2 *Carcinomas/
- 3 *Sarcomas/
- 4 *Lymphoma/
- 5 *Leukemia/
- 6 *Germ cell tumors/
- 7 metastas\$.mp. [mp=ti, ot, ab, nm, hw]
- 8 tumour\$.mp. [mp=ti, ot, ab, nm, hw]
- 9 tumor\$.mp. [mp=ti, ot, ab, nm, hw]
- 10 cancer\$.mp. [mp=ti, ot, ab, nm, hw]
- 11 neoplasm\$.mp. [mp=ti, ot, ab, nm, hw]
- 12 carcinoma\$.mp. [mp=ti, ot, ab, nm, hw]
- 13 lymphoma\$.mp. [mp=ti, ot, ab, nm, hw]
- 14 sarcoma\$.mp. [mp=ti, ot, ab, nm, hw]
- 15 leukemia\$.mp. [mp=ti, ot, ab, nm, hw]
- 16 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
OR #14 OR #15)
- 17 exp "Cost-Benefit Analysis"/
- 18 (value of life or economics, medical or economics, pharmaceutical or models,
economic or markov chains or monte carlo method or uncertainty).sh.
- 19 economics.fs.
- 20 economics.sh.
- 21 ((econom\$ or cost or costly or costing or costed or prices or pricing or discount or
discounts or discounted or discounting or budget\$ or afford\$ or
pharmacoeconomic\$ or pharmaco) adj1 economic\$).ti,ab.
- 22 (decision adj1 (tree\$ or analy\$ or model\$)).ti,ab.
- 23 (#17 OR # 18 OR #19 OR #20 OR #21 OR #22)
- 24 (Lynparza* or olaparib). mp. [mp=ti, it, ab, nm, hw]
- 25 (Talzenna* or talazoparib). mp. [mp=ti, it, ab, nm, hw]
- 26 (Rubraca* or rucaparib). mp. [mp=ti, it, ab, nm, hw]
- 27 (Iressa* or gefitinib). mp. [mp=ti, it, ab, nm, hw]
- 28 (Gilotrif* or afatinib). mp. [mp=ti, it, ab, nm, hw]
- 29 (Vizimpro* or dacomitinib). mp. [mp=ti, it, ab, nm, hw]
- 30 (Tarceva* or erlotinib). mp. [mp=ti, it, ab, nm, hw]
- 31 (Tagrisso* or osimertinib). mp. [mp=ti, it, ab, nm, hw]

- 32 (Keytruda* or pembrolizumab). mp. [mp=ti, it, ab, nm, hw]
- 33 (Tecentriq* or atezolizumab). mp. [mp=ti, it, ab, nm, hw]
- 34 (Tibsovo* or ivosidenib). mp. [mp=ti, it, ab, nm, hw]
- 35 (Tasigna* or nilotinib). mp. [mp=ti, it, ab, nm, hw]
- 36 (Alecensa* or alectinib). mp. [mp=ti, it, ab, nm, hw]
- 37 (Xalkori* or crizotinib). mp. [mp=ti, it, ab, nm, hw]
- 38 (Zykadia* or ceritinib). mp. [mp=ti, it, ab, nm, hw]
- 39 (Tafinlar* or dabrafenib). mp. [mp=ti, it, ab, nm, hw]
- 40 (Mekinist* or trametinib). mp. [mp=ti, it, ab, nm, hw]
- 41 (Zelboraf* or vemurafenib). mp. [mp=ti, it, ab, nm, hw]
- 42 (Cotellic* or cobimetinib). mp. [mp=ti, it, ab, nm, hw]
- 43 (Herceptin* or trastuzumab). mp. [mp=ti, it, ab, nm, hw]
- 44 (Perjeta* or pertuzumab). mp. [mp=ti, it, ab, nm, hw]
- 45 (Kadcyla* or ado-trastuzumab emtansine)
- 46 (Erbix* or cetuximab)
- 47 (Vectibix* or panitumumab)
- 48 (Idhifa* or enasidenib)
- 49 (Venclexta* or venetoclax)
- 50 (Gleevec* or Gilvec* or imatinib mesylate)
- 51 (Exjade* or deferasirox)
- 52 (#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51)
- 53 (#16 AND #23 AND #52)
- 54 Limits: humans, full-text, English, 5-year (2014-present)

Database: Embase

- 1 exp neoplasm
- 2 (neoplasm\$) OR (metastasis\$) OR (carcinoma\$) OR (sarcoma\$) OR (lymphoma\$) OR (leukemia) OR (germ adj3 cell adj3 tumor\$) OR (tumor\$) OR (cancer\$)
- 3 (#1 OR #2)
- 4 exp health economics/ or exp economic evaluation/ or exp "cost benefit analysis"/ or exp economic aspect/
- 5 (cost\$ adj2 effective\$) OR (cost\$ adj2 benefit\$) OR (cost\$ adj2 utility\$) OR (willingness to pay or net benefit\$) OR (economic\$ adj2 evaluation\$)
- 6 (decision adj2 (tree\$ or analysis\$ or model\$))
- 7 (#4 OR #5 OR #6)

- 8 (Lynparza* or olaparib)
- 9 (Talzenna* or talazoparib)
- 10 (Rubraca* or rucaparib)
- 11 (Iressa* or gefitinib)
- 12 (Gilotrif* or afatinib)
- 13 (Vizimpro* or dacomitinib)
- 14 (Tarceva* or erlotinib)
- 15 (Tagrisso* or osimertinib)
- 16 (Keytruda* or pembrolizumab)
- 17 (Tecentriq* or atezolizumab)
- 18 (Tibsovo* or ivosidenib)
- 19 (Tasigna* or nilotinib)
- 20 (Alecensa* or alectinib)
- 21 (Xalkori* or crizotinib)
- 22 (Zykadia* or ceritinib)
- 23 (Tafinlar* or dabrafenib)
- 24 (Mekinist* or trametinib)
- 25 (Zelboraf* or vemurafenib)
- 26 (Cotellic* or cobimetinib)
- 27 (Herceptin* or trastuzumab)
- 28 (Perjeta* or pertuzumab)
- 29 (Kadcyla* or ado-trastuzumab emtansine)
- 30 (Erbix* or cetuximab)
- 31 (Vectibix* or panitumumab)
- 32 (Idhifa* or enasidenib)
- 33 (Venclexta* or venetoclax)
- 34 (Gleevec* or Gilvec* or imatinib mesylate)
- 35 (Exjade* or deferasirox)
- 36 (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR
#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR
#30 OR #31 OR #32 OR #33 OR #34 OR #34 OR #35)
- 37 (#3 AND #7 AND #36)
- 38 Limits: humans, full-text, English, 5-year (2014-present)

Database: Econlit

1. biomark\$ OR (molecu\$ adj3 mark\$) OR (tumo?r adj3 mark\$) OR (biologic\$ adj3 mark\$)
OR (signature adj3 molecule\$)

2. (target adj3 therap\$) OR (targeted adj3 therap\$) OR (personalized adj3 medicine\$) OR (companion adj3 diagnostic\$ OR (precision adj3 medicine\$) OR (codependent adj3 technolog\$)
3. neoplasm\$ OR metatas\$ OR carcinoma\$ OR sarcoma\$ OR lymphoma\$ OR leukemia OR (germ adj3 cell adj3 tumor\$) OR tumor\$ OR cancer\$
4. Lynparza\$ or olaparib
5. Talzena\$ or talazoparib
6. Rubraca\$ or rucaparib
7. Iressa\$ or gefitinib
8. Gilotrif\$ or afatinib
9. Vizimpro\$ or dacomitinib
10. Tarceva\$ or erlotinib
11. Tagrisso\$ or osimertinib
12. Keytruda\$ or pembrolizumab
13. Tecentriq\$ or atezolizumab
14. Tibsovo\$ or ivosidenib
15. Tasigna\$ or nilotinib
16. Alecensa\$ or alectinib
17. Xalkori\$ or crizotinib
18. Zykadia\$ or ceritinib
19. Tafinlar\$ or dabrafenib
20. Mekinist\$ or trametinib
21. Zelboraf\$ or vemurafenib
22. Cotellic\$ or cobimetinib
23. Herceptin\$ OR trastuzumab
24. Perjeta\$ or pertuzumab
25. Kadcyla\$ OR ado-trastuzumab emtansine
26. Erbitux\$ OR cetuximab
27. Vectibix\$ OR panitumumab
28. Idhifa\$ OR enasidenib
29. Venclexta\$ or venetoclax
30. Gleevec\$ or Gilvec\$ or imatinib mesylate
31. Exjade\$ or deferasirox
32. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31)
33. Limits: full-text, period (2014 to current)

Database: Cochrane via Wiley (technology assessments and economic evaluations)

1. MeSH descriptor: [Neoplasms] explode all trees
2. MeSH descriptor: [Sarcoma] explode all trees
3. MeSH descriptor: [Lymphoma] explode all trees
4. MeSH descriptor: [Leukemia] explode all trees
5. (neoplasm\$) OR (metatas\$) OR (carcinoma\$) OR (sarcoma\$) OR (lymphoma\$) OR (leukemia) OR (germ adj3 cell adj3 tumor\$) OR (tumo?r\$) OR (cancer\$)
6. (#1 OR #2 OR #3 OR #4 OR #5)
7. MeSH descriptor: [Costs and Cost Analysis] explode all trees
8. MeSH descriptor: [Cost-Benefit Analysis] explode all trees
9. MeSH descriptor: [Economics, Pharmaceutical] explode all trees
10. (cost effective\$) OR (cost benefit\$) OR (cost utility\$) OR (economic evaluation\$)
11. (#7 OR #8 OR #9 OR #10)
12. Lynparza\$ or olaparib OR Talzena\$ or talazoparib OR Rubraca\$ or rucaparib OR Iressa\$ or gefitinib OR Gilotrif\$ or afatinib OR Vizimpro\$ or dacomitinib OR Tarceva\$ or erlotinib OR Tagrisso\$ or osimertinib OR Keytruda\$ or pembrolizimab OR Tecentriq\$ or atezolizumab OR Tibsovo\$ or ivosidenib OR Tassigna\$ or nilotinib OR Alecensa\$ or alectinib OR Xalkori\$ or crizotinib OR Zykadia\$ or ceritinib OR Tafinlar\$ or dabrafenib OR Mekinist\$ or trametinib OR Zelboraf\$ or vemurafenib OR Cotellic\$ or cobimetinib OR Herceptin\$ OR trastuzumab OR Perjeta\$ or pertuzumab OR Kadcyla\$ OR ado-trastuzumab emtansine OR Erbitux\$ OR cetuximab OR Vectibix\$ OR panitumumab OR Idhifa\$ OR enasidenib OR Venclexta\$ or venetoclax OR Gleevec\$ or Gilvec\$ or imatinib mesylate OR Exjade\$ or deferasirox
13. (#6 AND #11 AND #12)
14. Limits: publication from Jan 2014 to Dec 2018. Cochrane protocols, Clinical answers, Editorials

APPENDIX 3- 2 : PICOS AND INCLUSION/EXCLUSION CRITERIA

PICOS	Inclusion criteria	Exclusion criteria
Population	Adult patients (≥ 16 years) with cancer treated with biomarker-guided therapies	Patients < 16 years
Intervention	Precision medicine Personalized medicine Biomarker-guided therapies Companion diagnostic devices Cancer biomarkers for targeted therapies	No companion diagnostics No predictive biomarkers for targeted therapies No biomarker-guided therapies Drugs without assessing companion biomarkers Universal screening tools Triage procedures Severity or progression analyses
Comparator	Unrestricted	No comparative treatment Surgery
Outcome	Biomarker characteristics Methodological approaches Modelling inputs	-
Study type	Full-text economic evaluations (cost-effectiveness analysis, cost-utility analysis)	Abstract No economic evaluations No English Costing studies Cost-minimization studies

Selection of papers followed the eligibility criteria below:

Population: adult patients with cancer tested with companion biomarkers for targeted therapies. Studies conducted on pre-specified patients with a biomarker status confirmed were excluded if they did not consider any of biomarker-related characteristics in their evaluations.

Intervention: companion biomarkers for targeted anti-cancer therapies. These biomarkers are used as diagnostic tools to guide the optimal treatment option(s) for patients responsive or unresponsive to the corresponding therapeutic products. Biomarker tests without market authorizations co-licensed with companion therapeutic products were not of interest in this review.

Comparator: conventional treatments (e.g. chemotherapy, best supportive care) or targeted therapies with or without the use of companion biomarker tests.

Outcome: Methodological or modelling approaches, biomarker characteristics, data inputs of biomarker tests. Studies without sufficient information reported on these items (e.g. abstracts) were excluded.

Study type: economic evaluations including model or trial-based analyses.

APPENDIX 3-3 : LIST OF INCLUDING THE CHARACTERISTICS OF COMPANION BIOMARKERS IN THE ECONOMIC EVALUATIONS

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7.1	Q7.2	Q8	Q9	Q10	Q11	Q12
Aguiar 2017 (125)	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	No	Yes	No
Chouaid 2017 (126)	No	Yes	No	No	No	No	No	Yes	No	No	Yes	No	No
Curl 2014 (127)	No	Yes	Yes	No	No	No	No	Yes	No	No	Yes	Yes	No
Ewara 2014 (102)	No	Yes	Yes	No	No	No	No	No	No	No	Yes	No	No
Graham 2014 (87)	No	Yes	No	No	No	No	No	Yes	No	No	Yes	Yes	Yes
Graham 2016 (128)	No	Yes	No	No	No	No	No	Yes	No	No	Yes	Yes	No
Harty 2018 (129)	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	Yes	No
Huxley 2017 (130) Tikhonova 2018 (134)	No	Yes	Yes	No	No	No	No	Yes	No	Yes	Yes	No	Yes
Janmaat 2016 (131)	No	Yes	Yes	No	No	No	No	Yes	No	Yes	No	No	Yes
Lim 2016 (135)	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes
Lu 2018 (136)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Morgan 2017 (132)	No	Yes	Yes	No	No	No	No	Yes	No	No	Yes	Yes	No
Wen 2015 (69)	Yes	Yes	No	Yes	No	No	No	Yes	No	No	No	Yes	No
Westwood 2014 (137)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Wu 2017 (133)	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	Yes	Yes
Zhou 2016 (72)	Yes	Yes	No	No	No	No	No	Yes	No	No	Yes	No	No
Saito 2017 (68)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes
Butzke 2016 (118)	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	No	No

APPENDIX 4-1 : SUMMARY OF PATIENT CHARACTERISTICS

	Bevacizumab trial ¹	Dacarbazine trial ²
Number of study cohort	N = 35	N = 338
Median age (range)	63 (26 – 77)	52 (17 – 86)
ECOG performance status – no. (%)		
0	28 (80)	230 (68)
1	7 (20)	108 (32)
Male sex – no. (%)	19 (54)	181 (54)

¹ Schuster C, Eikesdal HP, Puntervoll H, Geisler J, Geisler S, et al. (2012) Clinical efficacy and safety of bevacizumab monotherapy in patients with metastatic melanoma: predictive importance of induced early hypertension. PLoS ONE 7(6): e38364. Doi:10.1371/journal.pone.0038364

² McArthur GA, Chapman PB, Robert C, Larkin J, Haanen JB, Dummer R et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol. 2014;15(3):323-32. doi: 10.1016/S1470-2045(14)70012-9. Epub 2014 Feb 7.

APPENDIX 4-2 : PARAMETERS USED IN THE MODEL

(DACARBAZINE)

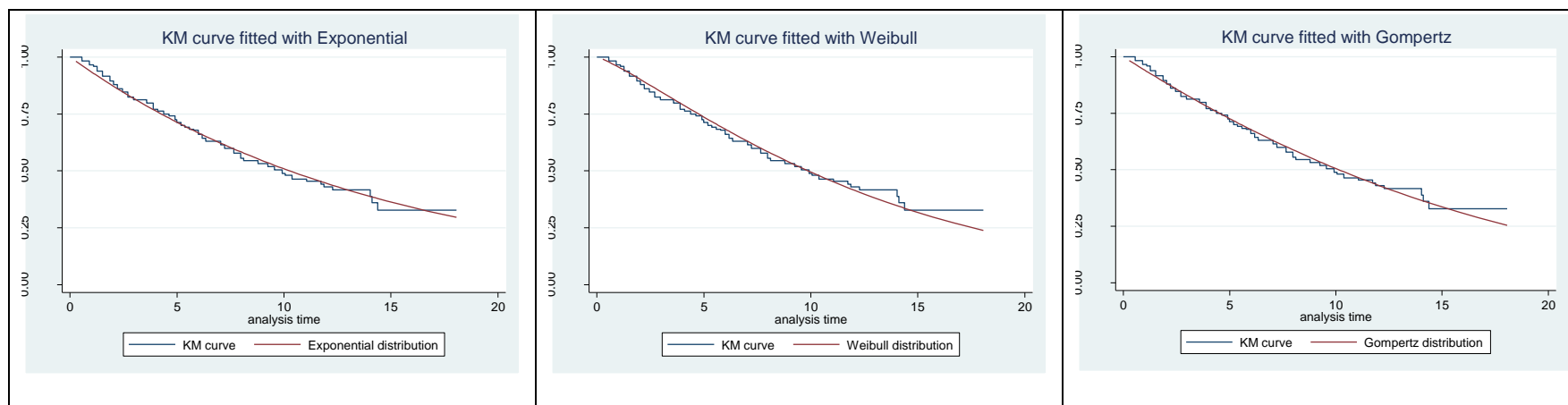
KM curve	Distribution	Survival function	Parameters used in the model
OS	Log-normal	$S(t) = 1 - \Phi\left(\frac{\log(t) - \mu}{\sigma}\right)$	$\mu = 2.279977$ $\sigma = 1.222045$
PFS	Ggamma	$S(t) = 1 - I(\kappa - 2, \kappa - 2e^{\kappa((\log(t) - \mu)/\sigma)})$ ($\kappa > 0$)	$k = -.9470793$ $\mu = .6701823$ $\sigma = .8424385$

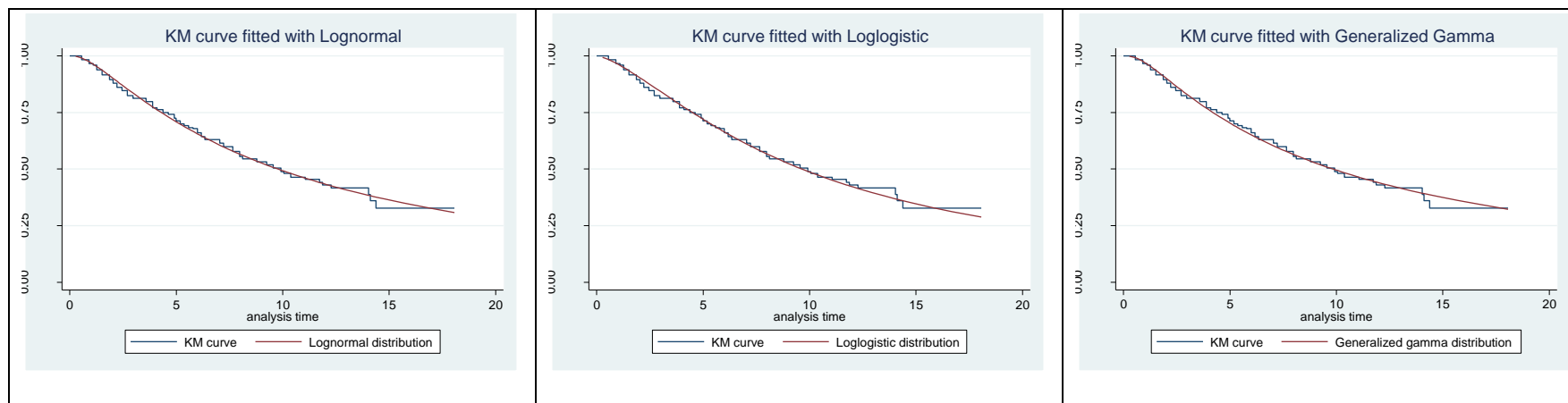
(Beverizumab)

KM curve	Distribution	Survival function	Parameters used in the model
OS	Gompertz	$S(t) = e^{-\left(\frac{\lambda}{\gamma}\right)(e^{\gamma t} - 1)}$	$\lambda = 0.2072661$ $\gamma = -0.124534$
PFS	Log-normal	$S(t) = 1 - \Phi\left(\frac{\log(t) - \mu}{\sigma}\right)$	$\mu = 1.645146$ $\sigma = 1.48675$

APPENDIX 4-3 : VISUAL INSPECTION, AIC AND BIC RESULTS WHEN PARAMETRIC SURVIVAL DISTRIBUTIONS FITTED TO THE KM CURVES

A. Overall survival of Dacarbazine: Model fits for Kaplan-Meier curve by different distributions and AIC/BIC results

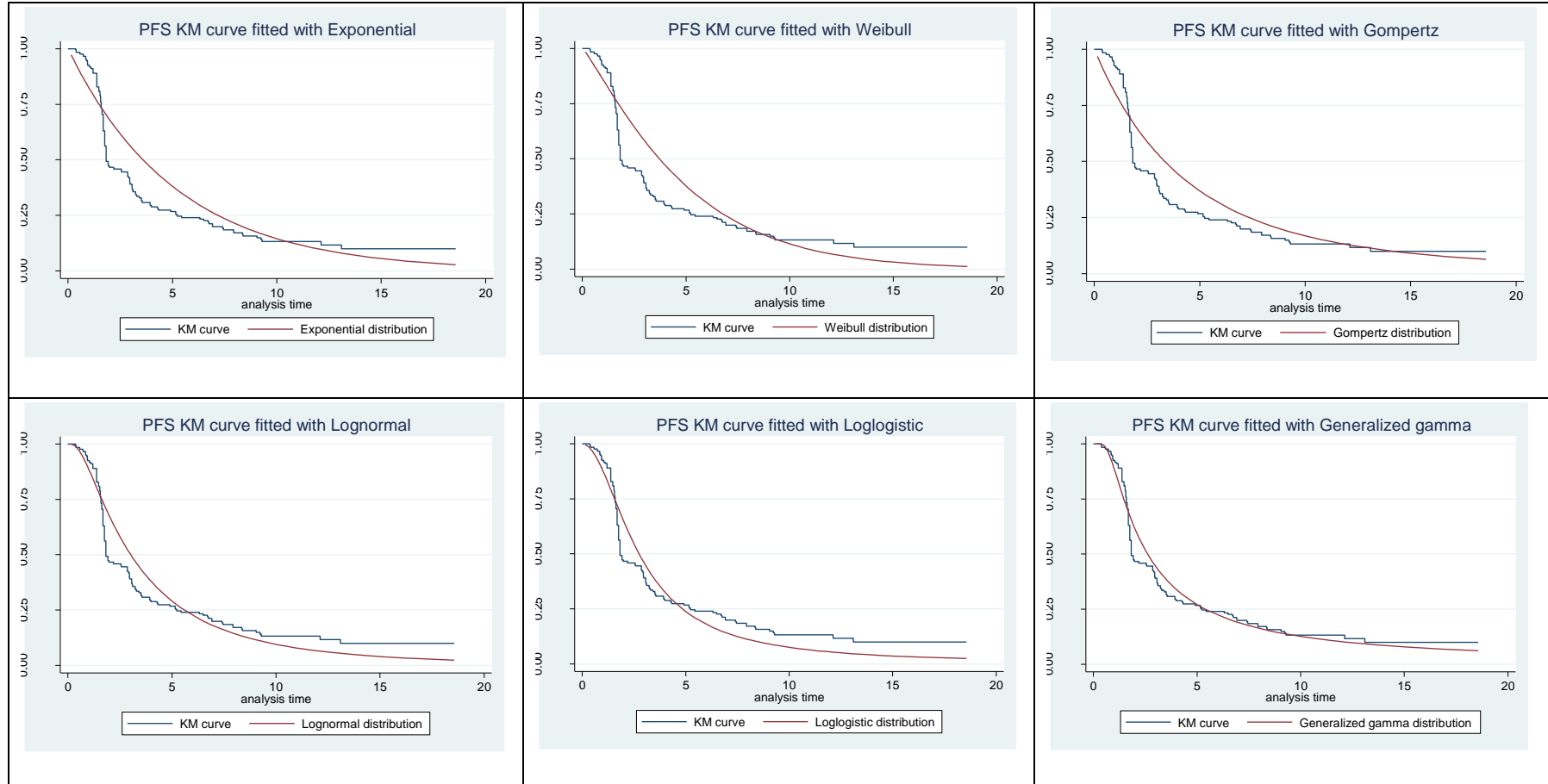




Fitted distributions for OS KM data	AIC	BIC
Exponential	625.7581	629.5812
Weibull	621.7382	629.3843
Gompertz	626.7534	634.3995
Log-normal	612.4530	620.0991
Log-logistic	617.1194	624.7654
Ggamma	614.1587	625.6278

AIC; Akaike information criterion, BIC; Bayesian information criterion

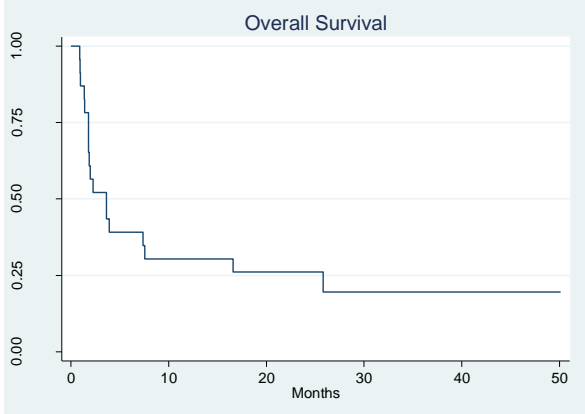
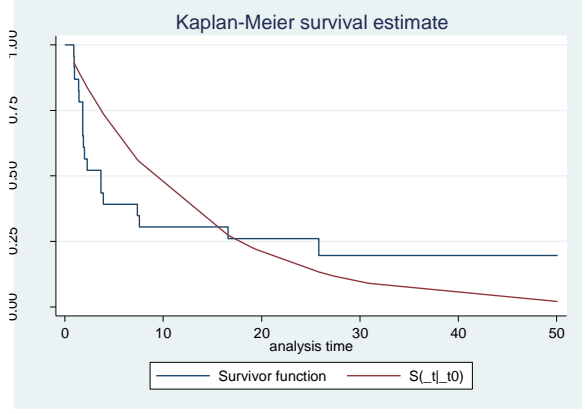
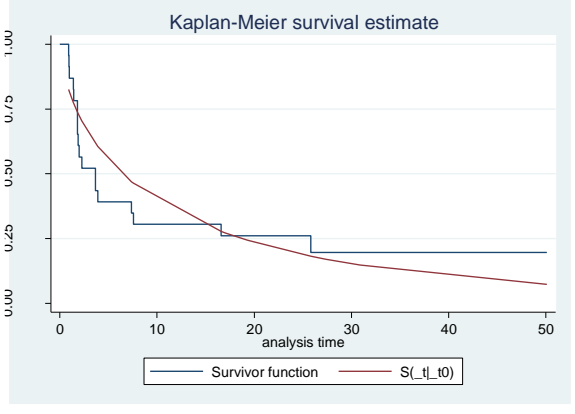
B. Progression-Free Survival of Dacarbazine: Model fits for Kaplan-Meier curve by different distributions and AIC/BIC results

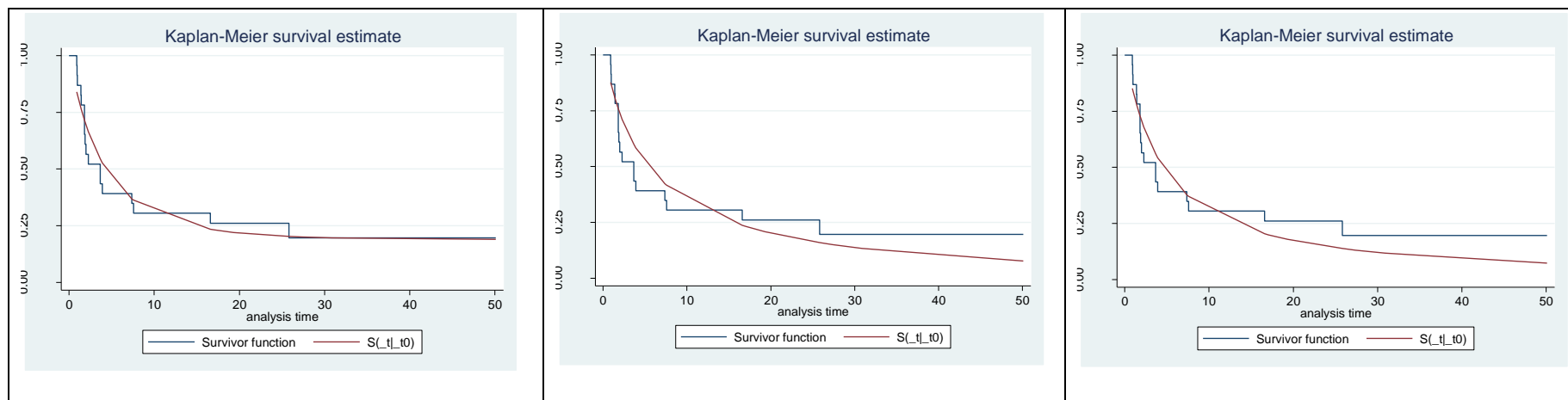


Fitted distributions for PFS KM data	AIC	BIC
Exponential	497.2788	501.1018
Weibull	493.1551	500.8012
Gompertz	495.8613	503.5074
Log-normal	434.8525	442.4986
Log-logistic	436.7084	444.3545
Ggamma	414.4038	425.8729

AIC; Akaike information criterion, BIC; Bayesian information criterion

C. Overall survival of Bevacizumab (HSP27 positive): Model fits for Kaplan-Meier curve by different distributions and AIC/BIC results

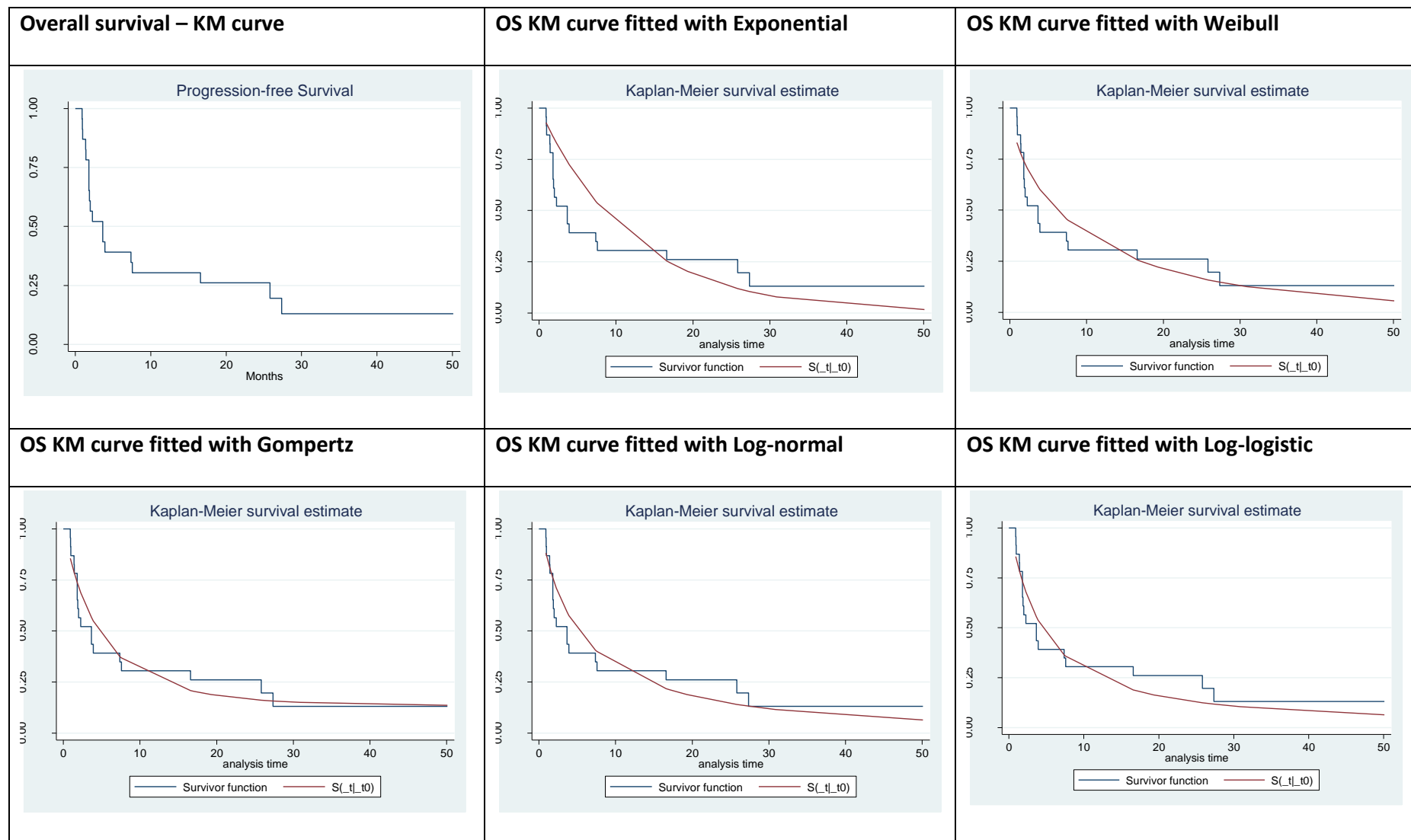
Overall survival – KM curve	OS KM curve fitted with Exponential	OS KM curve fitted with Weibull
		
OS KM curve fitted with Gompertz	OS KM curve fitted with Log-normal	OS KM curve fitted with Log-logistic



Fitted distributions for OS KM data	AIC	BIC
Exponential	93.06797	94.20347
Weibull	88.46272	90.7337
Gompertz	81.27416	83.54515
Log-normal	81.97873	84.24971
Log-logistic	84.24971	84.918

AIC; Akaike information criterion, BIC; Bayesian information criterion

D. Progression-Free Survival of Bevacizumab (HSP27 positive): Model fits for Kaplan-Meier curve by different distributions and AIC/BIC results

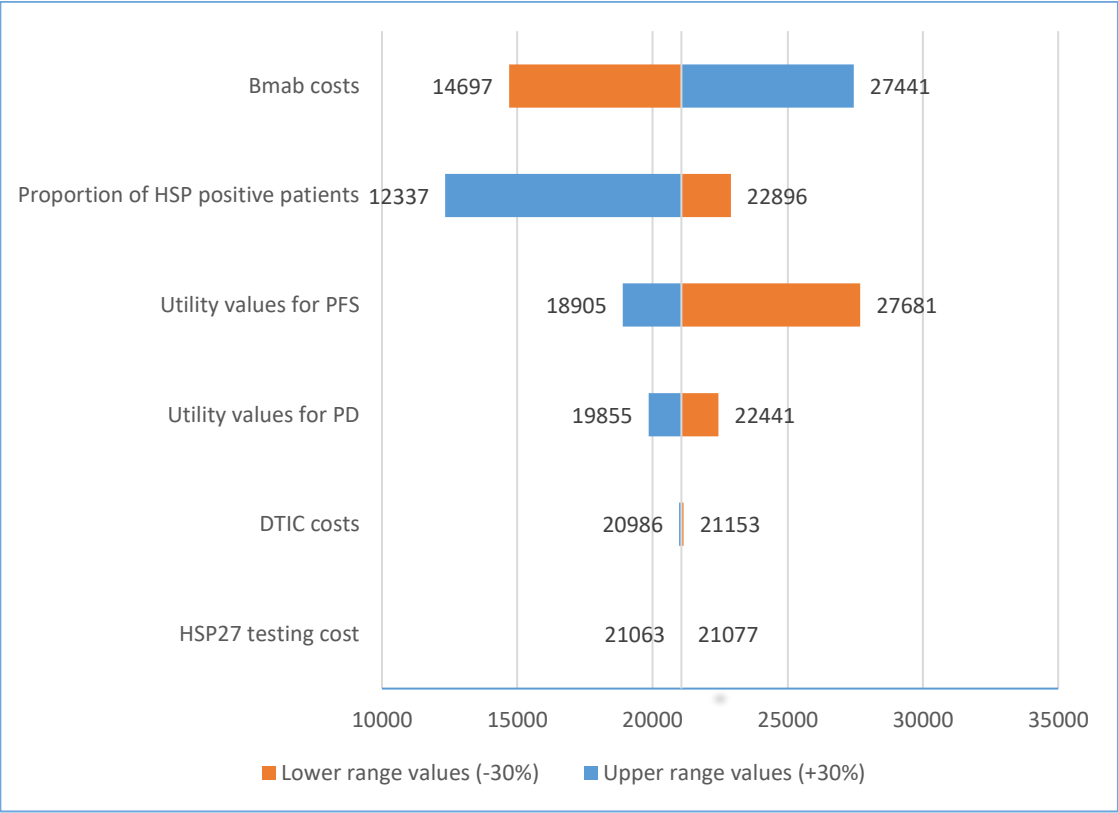


APPENDIX 4-4 : ROC ANALYSIS RESULTS: COMBINATION OF DECISION THRESHOLDS PER HSP27 STAINING

INDEX

HSP27 index	1-specificity (x-axis)	Sensitivity (y-axis)
1	-	-
2	100.0%	100.0%
3	95.8%	90.9%
4	58.3%	81.8%
5	50.0%	72.7%
6	50.0%	72.7%
7	12.5%	36.4%
8	12.5%	36.4%
9	12.5%	36.4%
10	0.0%	0.0%

APPENDIX 4-5 : TORNADO DIAGRAM



APPENDIX 4-6: THE PATHOLOGIC TUMOUR-NODE-METASTATES (PTNM) CLASSIFICATION (SOURCED FROM SCHUSTER PHD THESIS¹)

▪ **T-classification in cutaneous melanoma**

T* classification	Thickness (mm)	Ulceration/mitosis
T1	≤ 1.0	a: +/- ulceration and mitosis < 1/mm ² b: + ulceration and mitosis ≥ 1/mm ²
T2	1.01 – 2.0	a: +/- ulceration b: + ulceration
T3	2.01 – 4.0	a: +/- ulceration b: + ulceration
T4	> 4.0	a: +/- ulceration b: + ulceration

* Primary tumours (T) are classified by tumour thickness and the absence or presence of tumour ulceration.

¹Schuster C. Investigation of predictive markers in patients with metastatic melanoma treated with bevacizumab (PhD thesis): University of Bergen, Bergen, Norway; 2016.

▪ **N-classification in cutaneous melanoma**

N* classification	Number of metastatic nodes	Nodal metastatic burden
N0	0	Not applicable
N1	1	a: micrometastases [#] b: macrometastases [^]
N2	2 – 3	a: micrometastases [#] b: macrometastases [^]
N3	4+ or matted nodes or in transit met/satellites with metastatic nodes	c: in transit metastases or satellites without metastatic nodes

*Node (N)-stage is defined by the number of affected regional lymph nodes and include in transit metastases and microscopic satellites.

¹Schuster C. Investigation of predictive markers in patients with metastatic melanoma treated with bevacizumab (PhD thesis): University of Bergen, Bergen, Norway; 2016.

▪ M-classification in cutaneous melanoma

M* classifications	Site	Serum LDH
0	No distant metastases	Not applicable
M1a	Distant skin, subcutaneous or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases Any distant metastases	Normal Elevated

*Metastases (M) -categories are defined by the site of distant metastases and serum levels of lactate dehydrogenase (LDH).

APPENDIX 5-1 : R CODES FOR STEP 1. TRANSITION PROBABILITY

```
a. Vectoring probability data inputs in R
  eff <- 0.25 #Efficacy of targeted therapy compared to usual care.
  pPFS2PD.UC <- 0.2 #transition probability from PFS to PD when treated with UC.
  pPFS2PD.TC <- 0.2 - (0.2*eff) #transition probability from PFS to PD when treated with TC.
  pPD2D <- 0.25 #transition probability from PD to Dead.
  pPFS2D <- 0.05 #transition probability from PFS to Dead.
  state_names <- c("PFS", "PD", "Dead") #names of health states.
  n.states <- length(state_names) #number of health states.

b. Creating transition matrix of PFS for all-UC arm
  t.PFS.UC <- numeric()
  t.PFS.UC[2] <- pPFS2PD.UC
  t.PFS.UC[3] <- pPFS2D
  t.PFS.UC[1] <- 1 - sum(t.PFS.UC[-1])

c. Creating transition matrix of PFS for all-TC arm
  t.PFS.UC <- numeric()
  t.PFS.UC[2] <- pPFS2PD.UC
  t.PFS.UC[3] <- pPFS2D
  t.PFS.UC[1] <- 1 - sum(t.PFS.UC[-1])

d. Creating transition matrix of health state PD
  t.PD <- numeric()
  t.PD[1] <- 0
  t.PD[3] <- pPD2D
  t.PD[2] <- 1 - sum(t.PD[-2])

e. Creating transition matrix of health state Dead
  t.Dead <- c(0,0,1)
```

- f. Creating transition matrix for patients treated with biomarker non-guided therapy (also referred to as ‘usual care’)
- ```
pTransition.UC <- matrix(c(t.PFS.UC, t.PD, t.Dead),
 nrow = 3, ncol = 3, byrow = TRUE,
 dimnames = list(state_names, state_names))
```
- g. Creating transition matrix for patients treated with biomarker-guided therapy (also referred to as ‘targeted care’)
- ```
pTransition.TC <- matrix(c(t.PFS.TC, t.PD, t.Dead),
                        nrow = 3, ncol = 3, byrow = TRUE,
                        dimnames = list(state_names, state_names))
```
- h. Double check if transition probabilities add up to 1
- ```
rowSums(pTransition.UC)
rowSums(pTransition.TC)
```

## APPENDIX 5-2 : R CODES FOR STEP 2. COST AND UTILITY

- a. Vectoring cost data inputs
- ```
cPFS <- 500   #costs in health state of PFS.
cPD <- 3000   #costs in health state of PD.
cDead <- 0     #costs in health state of Dead.
cDrug <- 1000  #costs of targeted therapy.
cTest <- 100   #costs of biomarker testing.
```
- b. Preparing cost transition matrices
- ```
cTransition.UC <- c(cPFS, cPD, cDead) #for patients treated with UC.
names(cTransition.UC) <- state_names
cTransition.TC <- c(cPFS + cDrug, cPD, cDead) #treated with TC.
names(cTransition.TC) <- state_names

cTransition.TTC <- c(cPFS + cDrug + cTest, cPD, cDead) # test-treated with TC, if test positive.
names(cTransition.TTC) <- state_names
cTransition.TUC <- c(cPFS + cTest, cPD, cDead) # test-treated with UC, if test negative.

names(cTransition.TUC) <- state_names
```
- c. **Vectoring utility data inputs**
- ```
uPFS.UC <- 0.75 #utility values for patients treated with UC while in PFS.
uPFS.TC <- 0.80 #utility values for patients treated with TC while in PFS.
uPD.UC <- 0.45 #utility values for patients treated with UC while in PD.
uPD.TC <- 0.65 #utility values for patients treated with TC while in PD.
uDead <- 0
```
- d. **Preparing utility transition matrices**
- ```
uTransition.UC <- c(uPFS.UC, uPD.UC, uDead) #patients treated with UC.
names(uTransition.UC) <- state_names
uTransition.TC <- c(uPFS.TC, uPD.TC, uDead) #treated with TC.
names(uTransition.TC) <- state_names
#Utility values for patients tested and biomarker positive confirmed and thus, treated with TC.
uTransition.TTC <- c(uPFS.TC - disutility.Test, uPD.TC, uDead)
```

```
names(uTransition.TTC) <- state_names
#Utility values for patients tested and biomarker negative confirmed and thus, treated with UC.
uTransition.TUC <- c(uPFS.UC - disutility.Test, uPD.UC, uDead)
names(uTransition.TUC) <- state_names
```

### APPENDIX 5-3 : R CODES FOR STEP 3. SIMULATION MODEL FOR ALL-UC ARM

- a. Vectoring data inputs for cohort trace
 

```
n.t <- 1000 #total number of cycles to run the Markov model.
pBiomarker <- 0.3 #prevalence/frequency of biomarker status.
pSensitivity <- 0.95 #biomarker testing accuracy – sensitivity.
pSpecificity <- 0.65 #biomarker testing accuracy – specificity.
tp <- pSensitivity #true positive.
fp <- 1- pSensitivity #false positive.
tn <- pSpecificity #true negative.
fn <- 1 - pSpecificity #false negative.
```
- b. Defining and initializing the matrix for all-UC arm
 

```
MT.UC <- matrix(NA, nrow = n.t + 1, ncol = n.states,
 dimnames = list(paste("Cycle", 0:n.t, sep = " "),
 state_names))
```
- c. Starting a hypothetical cohort of all patients from health state of PFS
 

```
MT.UC[1,] <- c(1000,0,0) #initiate first cycle of cohort trace in all-UC arm.
```
- d. Run the model for all-UC arm
 

```
for (t in 1:n.t) { #loop through the number of cycles.
 MT.UC[t+1,] <- t(MT.UC[t,]) %*% pTransition.UC
}
```

### APPENDIX 5-4 : R CODES FOR STEP 4. SIMULATION MODEL FOR ALL-TC, TEST-TREAT ARMS RESPECTIVELY

- a. Defining and initializing matrices and vectors for all-TC arm
 

```
MT.TTC <- MT.TUC <- matrix(NA, nrow = n.t + 1, ncol = n.states,
 dimnames = list(paste("Cycle", 0:n.t, sep = " "),
 state_names))
```
- b. Defining and initializing matrices and vectors for TT arms
 

```
MT.TTCtp <- MT.TTCfp <- MT.TUCtn <- MT.TUCfn <- matrix(NA, nrow = n.t + 1, ncol = n.states,
 dimnames = list(paste("Cycle", 0:n.t, sep = " "),
 state_names))
```
- c. Starting a hypothetical cohort of all patients from health state of PFS in all-TC arm
 

```
MT.TTC[1,] <- c(1*pBiomarker, 0,0) #initiate first cycle considering prevalence of biomarker status in allTC arm and patients were biomarker positive and thus, TC was effective.
MT.TUC[1,] <- c(1*(1-pBiomarker), 0,0) #initiate first cycle considering prevalence of biomarker status in all-TC arm and patients were biomarker negative and thus, TC was not effective.
```
- d. Starting a hypothetical cohort of all patients from health state of PFS in TT arm
 

```
MT.TTCtp[1,] <- c(1*pBiomarker*tp, 0, 0) #true positive patients.
MT.TTCfp[1,] <- c(1*pBiomarker*fp, 0, 0) #false positive patients.
MT.TUCtn[1,] <- c(1*(1-pBiomarker)*tn, 0, 0) #true negative patients.
```

```
MT.TUCfn[1,] <- c(1*(1-pBiomarker)*fn, 0, 0) #false negative patients.
```

- e. Run the model of all-TC arm

```
for (t in 1:n.t) { #loop through the number of cycles.
 MT.TUC[t+1,] <- t(MT.TUC[t,]) %*%pTransition.UC
 MT.TTC[t+1,] <- t(MT.TTC[t,]) %*%pTransition.TC
}
MT.allTC <- MT.TTC + MT.TUC #summing the cohort traces of MT.TTC and MT.TUC
```

- f. Run the model of TT arm

```
for (t in 1:n.t) {
 MT.TTCtp[t+1,] <- t(MT.TTCtp[t,]) %*%pTransition.TC
 MT.TTCfp[t+1,] <- t(MT.TTCfp[t,]) %*%pTransition.UC
 MT.TUCtn[t+1,] <- t(MT.TUCtn[t,]) %*%pTransition.UC
 MT.TUCfn[t+1,] <- t(MT.TUCfn[t,]) %*%pTransition.UC
} #loop through the number of cycles
```

## APPENDIX 5-5 : R CODES FOR STEP 5. COMPUTING EPIDEMIOLOGICAL OUTCOMES

- a. Creating survival curves of patients in all-UC arm

```
matplot(MT.UC, type = 'l', # "l" for lines, "p" for points.
 ylab = "Probability of state occupancy",
 xlab = "Cycle",
 main = "Cohort Trace of all-UC arm") #create a plot of the data.
legend("topright", state_names, #add a legend to the graph.
 col = 1:n.states, lty = 1:n.states, bty = "n")
#lty: line type. e.g lty=1 is solid line, lty=2 is dashed line
#bty: box type. default value bty = 0 or n
```

- b. Creating survival curves of patients in all-TC arm

```
MT.allTC <- MT.TTC + MT.TUC
matplot(MT.allTC, type = 'l',
 ylab = "Probability of state occupancy",
 xlab = "Cycle",
 main = "Cohort Trace of all-TC arm")
legend("topright", state_names,
 col = 1:n.states, lty = 1:n.states, bty = "n")
```

- c. Survival curves of patients in Test-Treat arm

```
MT.TT <- MT.TTCtp + MT.TTCfp + MT.TUCtn + MT.TUCfn
matplot(MT.TT, type = 'l',
 ylab = "Probability of state occupancy",
 xlab = "Cycle",
 main = "Cohort Trace of TT arm")
legend("topright", state_names,
 col = 1:n.states, lty = 1:n.states, bty = "n")
```

- d. Creating overall survival of all-UC arm

```
OS.UC <- 1 - MT.UC["Dead"]
#alternatively, use this code: OS.UC <- rowSums(MT.UC[, 1:2])
plot(OS.UC, type = 'l',
```

```

ylim = c(0, 1),
ylab = "Survival probability",
xlab = "Cycle",
main = "Overall Survival of all-UC arm")

#creating a plot showing OS curve
grid(nx = n.t, ny = 10, col = "lightgray", lty = "dotted", lwd = par("lwd"), equilogs = TRUE) # add
grid

e. Creating overall survival of all-TC arm
OS.allTC <- 1 - MT.allTC[, "Dead"]
plot(OS.allTC, type = 'l',
 ylim = c(0, 1),
 ylab = "Survival probability",
 xlab = "Cycle",
 main = "Overall Survival of all-TC arm")
grid(nx = n.t, ny = 10, col = "lightgray", lty = "dotted", lwd = par("lwd"), equilogs = TRUE)

f. Creating overall survival of TT arm
OS.TT <- 1 - MT.TT[, "Dead"]
plot(OS.TT, type = 'l',
 ylim = c(0, 1),
 ylab = "Survival probability",
 xlab = "Cycle",
 main = "Overall Survival of TT arm")
grid(nx = n.t, ny = 10, col = "lightgray", lty = "dotted", lwd = par("lwd"), equilogs = TRUE)

g. Estimating life expectancy (LE)
LE.UC <- sum(OS.UC) #LE of all-UC arm.
LE.allTC <- sum(OS.allTC) #LE of all-TC arm.
LE.TT <- sum(OS.TT) #LE of TT arm.

```

## APPENDIX 5-6 : R CODES FOR STEP 6. CALCULATING COST-EFFECTIVENESS

```

a. Estimating mean QALYs
uEV.UC <- MT.UC %*% uTransition.UC #QALY for allUC arm.
uEV.TTC <- MT.TTC %*% uTransition.TC #QALY for allTC arm but actually biomarker positive.
uEV.TUC <- MT.TUC %*% uTransition.UC #QALY for allTC arm but actually biomarker negative.

TT arm
uEV.TTCtp <- MT.TTCtp %*% uTransition.TTC #QALY for test positive and treated with TC.
uEV.TTCfp <- MT.TTCfp %*% uTransition.TUC #QALY for false positive and thus, TC is not effective
uEV.TUCtn <- MT.TUCtn %*% uTransition.TUC #QALY for true negative and treated with UC.
uEV.TUCfn <- MT.TUCfn %*% uTransition.TUC #QALY for false negative and thus, TC would be
better but UC was provided.

b. Estimating mean costs
cEV.UC <- MT.UC %*% cTransition.UC #Cost for all-UC arm.
cEV.allTC <- MT.allTC %*% cTransition.TC #Cost for all-TC arm.

#TT arm
cEV.TTCtp <- MT.TTCtp %*% cTransition.TTC #Cost for true positive and treated with TC.
cEV.TTCfp <- MT.TTCfp %*% cTransition.TTC #Cost for false positive and treated with TC.

```



```

cEV.TUCtn <- MT.TUCtn %*% cTransition.TUC #Cost for true negative and treated with UC.
cEV.TUCfn <- MT.TUCfn %*% cTransition.TUC #Cost for false negative and treated with UC.
cEV.TT <- cEV.TTCtp + cEV.TTCfp + cEV.TUCtn + cEV.TUCfn

```

c. Generating discounted QALYs

```

rDiscount <- 0.035 #equal discount for costs and QALYs by 3.5%
cycle_rDiscount <- 1/(1 + rDiscount)^(0:n.t) #calculate discount weights for each cycle

```

```

uEV.allUC <- t(uEV.UC) %*% cycle_rDiscount #all-UC arm QALY
uEV.TUC <- t(uEV.TUC) %*% cycle_rDiscount
uEV.TTC <- t(uEV.TTC) %*% cycle_rDiscount
uEV.allTC <- d.uEV.TUC + d.uEV.TTC #all-TC arm QALY

```

```

uEV.TTCtp <- t(uEV.TTCtp) %*% cycle_rDiscount
d.uEV.TTCfp <- t(uEV.TTCfp) %*% cycle_rDiscount
d.uEV.TUCtn <- t(uEV.TUCtn) %*% cycle_rDiscount
d.uEV.TUCfn <- t(uEV.TUCfn) %*% cycle_rDiscount
d.uEV.TT <- d.uEV.TTCtp + d.uEV.TTCfp + d.uEV.TUCtn + d.uEV.TUCfn #TT arm QALY.

```

d. Generating discounted costs

```

cEV.allUC <- t(cEV.UC) %*% cycle_rDiscount #all-UC arm Cost.
cEV.allTC <- t(cEV.allTC) %*% cycle_rDiscount #all-TC arm Cost.
cEV.TTCtp <- t(cEV.TTCtp) %*% cycle_rDiscount
cEV.TTCfp <- t(cEV.TTCfp) %*% cycle_rDiscount
cEV.TUCtn <- t(cEV.TUCtn) %*% cycle_rDiscount
cEV.TUCfn <- t(cEV.TUCfn) %*% cycle_rDiscount
cEV.TT <- d.cEV.TTCtp + d.cEV.TTCfp + d.cEV.TUCtn + d.cEV.TUCfn #TT arm Cost.

```

e. Base-case cost-effectiveness calculation

```

uEV <- c(d.uEV.allUC, d.uEV.allTC, d.uEV.TT)
cEV <- c(d.cEV.allUC, d.cEV.allTC, d.cEV.TT)

```

```

list(Cost = cEV,
 Effect = uEV) #Vectoring the calculated values of cEV and uEV

```

*#ICER calculation*

```

names.strategy <- c("all-UC", "all-TC", "Test-Treat")
table.ce <- data.frame(Strategy=names.strategy,
 Cost = cEV, Effect = uEV)
table.ce[order(table.ce$Cost, decreasing = FALSE),] #sort CE table by the order of Cost

```

```

icer <- data.frame(cEV,uEV)
icer.sort <- t(icer[order(table.ce$Cost, decreasing = FALSE),])

```

```

d.cost1 = icer.sort[1,2] - icer.sort[1,1]
d.cost2 = icer.sort[1,3] - icer.sort[1,2]
incr.cost <- c(0, d.cost1, d.cost2)

```

```

d.qaly1 = icer.sort[2,2] - icer.sort[2,1]
d.qaly2 = icer.sort[2,3] - icer.sort[2,2]
incr.qaly <- c(0,d.qaly1,d.qaly2)

```

```

icer1 = d.cost1/d.qaly1
icer2 = d.cost2/d.qaly2
icer <- c(0,icer1,icer2)
icer.sort1 <- icer.sort[1,]
icer.sort2 <- icer.sort[2,]

v.strategy <- c("all-UC", "Test-Treat", "all-TC")
v.outcome <- c("Cost", "Incr Costs", "QALY", "Incr QALY", "ICER (/QALY)")

table.icer <- matrix(c((icer.sort1),
 c(0, d.cost1, d.cost2),
 c(icer.sort2),
 c(0, d.qaly1, d.qaly2),
 nrow = 4, ncol = 4, byrow=FALSE))

icer.sort.cost <- c(0, d.cost1, d.cost2)
icer.sort.qaly <- c(0, d.qaly1, d.qaly2)
icer.sort.result <- c(0, d.cost1/d.qaly1, d.cost2/d.qaly2)

ICER.basecase <- format (matrix(c(icer.sort1,icer.sort.cost,icer.sort2,
 icer.sort.qaly, icer.sort.result),
 nrow = 5, ncol = 3, byrow = TRUE,
 dimnames = list(v.outcome, v.strategy)), digits = 2)

#Alternatively, ICER can be simply computed as below.
ICER_2allUC <- (d.cEV.TT - d.cEV.allUC)/(d.uEV.TT - d.uEV.allUC)
ICER_2allTC <- (d.cEV.TT - d.cEV.allTC)/(d.uEV.TT - d.uEV.allTC)
ICER_2allUC #ICER of TT compared to allUC arm.
ICER_2allTC #ICER of TT compared to allTC arm.

```

Example base-case ICER output in R

```

> ##### 03.4 ICER calculation
> ICER_2allUC <- (d.cEV.TT - d.cEV.allUC)/(d.uEV.TT - d.uEV.allUC)
> ICER_2allTC <- (d.cEV.TT - d.cEV.allTC)/(d.uEV.TT - d.uEV.allTC)

> ICER_2allUC #ICER of TT compared to allUC arm
 [,1]
[1,] 11660.24
> ICER_2allTC #ICER of TT compared to allTC arm
 [,1]
[1,] 10305.29

```

## APPENDIX 5-7 : R CODES FOR STEP 7. PERFORMING SENSITIVITY ANALYSIS

### a. Defining the PSA model run

```

psa.model.run <- function(eff, pPFS2PD.UC, pPD2D, pPFS2D,
 pBiomarker, pSensitivity, pSpecificity,
 cPFS, cPD, cTest,
 uPFS.UC, uPFS.TC, uPD.UC, uPD.TC)
{
source (appendix - basically, same as the base case analysis but assigning and selecting a
random value from the distributions around input parameters defined above as psa.model.run)
cost = list(costUC = d.cEV.allUC,
 costTC = d.cEV.allTC,

```

```

 costTT = d.cEV.TT)
qaly = list(qalyUC = d.uEV.allUC,
 qalyTC = d.uEV.allTC,
 qalyTT = d.uEV.TT)
psa_output <- data.frame(cost, qaly)
return(psa_output)
}

```

b. Sampling the parameters for PSA output

```

n.sim <- 1000 #PSA size
set.seed(1)
psa_eff <- rbeta(n.sim,0.1,0.3) #drug efficacy
psa_pPFS2PD.UC <- rbeta(n.sim, 34,136)
psa_pPD2D <- rbeta(n.sim,32,95)
psa_pPFS2D <- rbeta(n.sim, 41 ,770)
psa_pBiomarker <- rbeta(n.sim, 30, 69) #prevalence of biomarker
psa_pSensitivity <- rbeta(n.sim, 1.18, 0.06)
psa_pSpecificity <- rbeta(n.sim, 14, 7.7)
psa_cPFS <- rgamma(n.sim, 43, 12)
psa_cPD <- rgamma(n.sim, 43, 70)
psa_cTest <- rgamma(n.sim, 43, 2.34)
psa_uPFS.UC <- rbeta(n.sim, 9.92, 3.31)
psa_uPFS.TC <- rbeta(n.sim, 7.73, 1.93)
psa_uPD.UC <- rbeta(n.sim, 23, 28)
psa_uPD.TC <- rbeta(n.sim, 14, 7.7)

```

c. Running the PSA

```

for (i in 1:n.sim){

 psa.results[[i]] <- psa.model.run(psa_eff[[i]], psa_pPFS2PD.UC[[i]],
 psa_pPD2D[[i]], psa_pPFS2D[[i]],
 psa_pBiomarker[[i]],psa_pSensitivity[[i]],
 psa_pSpecificity[[i]],psa_cPFS[[i]],
 psa_cPD[[i]], psa_cTest[[i]],
 psa_uPFS.UC[[i]], psa_uPFS.TC[[i]],
 psa_uPD.UC[[i]], psa_uPD.TC[[i]])

}

```

d. Calculating incremental cost and qalys

```

psa.results_dataframe <- data.frame(Reduce(rbind,psa.results))

incCosts_TT_UC <- psa.results_dataframe[, "costTT"] – psa.results_dataframe[, "costUC"]
incCosts_TT_TC <- psa.results_dataframe[, "costTT"] – psa.results_dataframe[, "costTC"]
incQalys_TT_UC <- psa.results_dataframe[, "qalyTT"] – psa.results_dataframe[, "qalyUC"]
incQalys_TT_TC <- psa.results_dataframe[, "qalyTT"] – psa.results_dataframe[, "qalyTC"]
incCosts_TC_UC <- psa.results_dataframe[, "costTC"] – psa.results_dataframe[, "costUC"]
incQalys_TC_UC <- psa.results_dataframe[, "qalyTC"] – psa.results_dataframe[, "qalyUC"]

summary(incCosts_TT_UC)
summary(incCosts_TT_TC)
summary(incCosts_TC_UC)

```

```
summary(incQalys_TT_TC)
summary(incQalys_TT_UC)
summary(incQalys_TC_UC)
```

e. Calculating ICER

```
psaICER_TT_UC = mean(incCosts_TT_UC)/mean(incQalys_TT_UC)
psaICER_TT_TC = mean(incCosts_TT_TC)/mean(incQalys_TT_TC)
psaICER_TC_UC = mean(incCosts_TC_UC)/mean(incQalys_TC_UC)
lambda <- 5000 #Willingness to pay threshold
incNB <- incQalys_TT_UC*lambda - incCosts_TT_UC
summary(incNB)
```

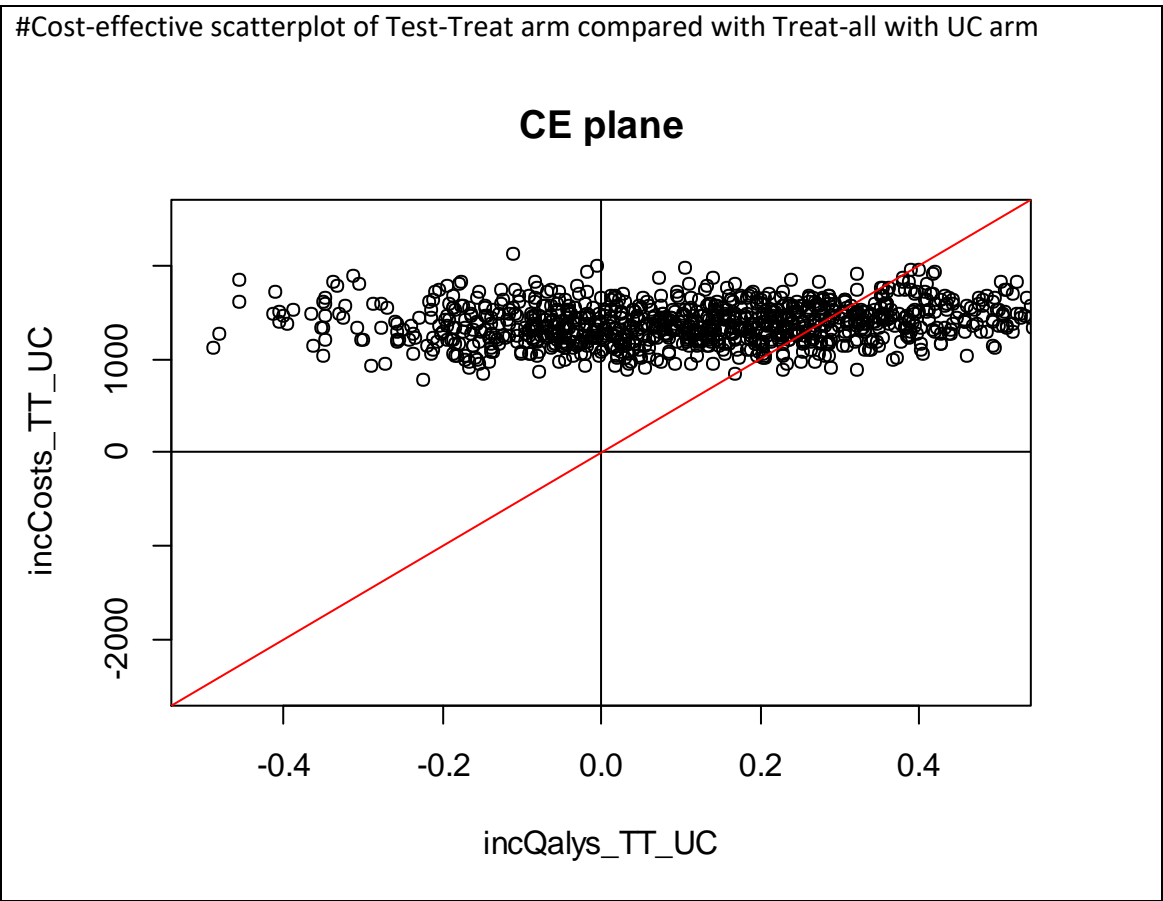
f. Plotting the CE plane

```
#CE plane of TT compared with all-UC strategy
plot(incCosts_TT_UC ~ incQalys_TT_UC, ylim = c(-0.5, 0.5) * lambda, xlim = c(-0.5, 0.5), main =
"CE plane")
abline(h = 0)
abline(v = 0)
abline(0, lambda, col = 2)

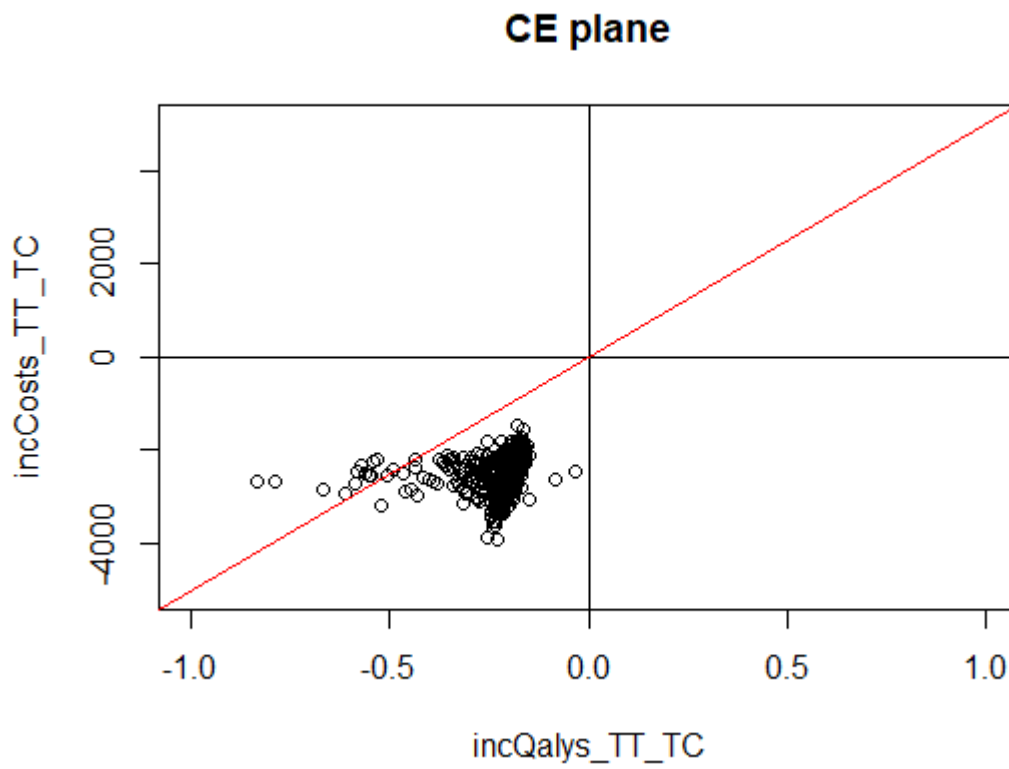
#CE plane of TT compared with all-TC strategy
plot(incCosts_TT_TC ~ incQalys_TT_TC, ylim = c(-1, 1) * lambda, xlim = c(-1, 1), main = "CE plane")
abline(h = 0)
abline(v = 0)
abline(0, lambda, col = 2)

#CE plane of all-TC compared with all-UC strategy
plot(incCosts_TC_UC ~ incQalys_TC_UC, ylim = c(-1.3, 1.3) * lambda, xlim = c(-1.3, 1.3), main =
"CE plane")
abline(h = 0)
abline(v = 0)
abline(0, lambda, col = 2)
```

Example PSA output in R



#Cost-effective scatterplot of Test-Treat arm compared with Treat-all with UC arm



#### Supplementary R codes for DSA simulation

##### *#1. Assign parameters for DSA simulation*

```
dsa_rate <- 0.3 #discount rate
dsa_eff <- c(eff*(1-dsa_rate), eff*(1+dsa_rate))
dsa_pPFS2PD.UC <- c(pPFS2PD.UC*(1-dsa_rate), pPFS2PD.UC*(1+pPFS2PD.UC))
dsa_pPD2D <- c(pPD2D*(1-dsa_rate), pPD2D*(1+dsa_rate))
dsa_pPFS2D <- c(pPFS2D*(1-dsa_rate), pPFS2D*(1+dsa_rate))
dsa_pBiomarker <- c(pBiomarker*(1-dsa_rate), pBiomarker*(1+dsa_rate))
dsa_pSensitivity <- c(pSensitivity*(1-dsa_rate), pSensitivity*(1+dsa_rate))
dsa_pSpecificity <- c(pSpecificity*(1-dsa_rate), pSpecificity*(1+dsa_rate))
dsa_cPFS <- c(cPFS*(1-dsa_rate), cPFS*(1+dsa_rate))
dsa_cPD <- c(cPD*(1-dsa_rate), cPD*(1+dsa_rate))
dsa_cTest <- c(cTest*(1-dsa_rate), cTest*(1+dsa_rate))
dsa_uPFS.UC <- c(uPFS.UC*(1-dsa_rate), uPFS.UC*(1+dsa_rate))
dsa_uPFS.TC <- c(uPFS.TC*(1-dsa_rate), uPFS.TC*(1+dsa_rate))
dsa_uPD.UC <- c(uPD.UC*(1-dsa_rate), uPD.UC*(1+dsa_rate))
dsa_uPD.TC <- c(uPD.TC*(1-dsa_rate), uPD.TC*(1+dsa_rate))
```

##### *#2. Define the DSA model run*

```
dsa.model.run <- function(eff)
dsa.model.run <- function(pPFS2PD.UC)
dsa.model.run <- function(pPD2D)
dsa.model.run <- function(pPFS2D)
dsa.model.run <- function(pBiomarker)
```

```

dsa.model.run <- function(pSensitivity)
dsa.model.run <- function(pSpecificity)
dsa.model.run <- function(cPFS)
dsa.model.run <- function(cPD)
dsa.model.run <- function(cTest)
dsa.model.run <- function(uPFS.UC)
dsa.model.run <- function(uPFS.TC)
dsa.model.run <- function(uPD.UC)
dsa.model.run <- function(uPD.TC)
{

#3. Repeat model run used in Step 6.

#4. Generate the OWSA results
dsa.results1 <- list() #Set up an empty dataframe for results.
for (i in 1:2) {
 dsa.results1 [[i]] <- dsa.model.run(dsa_eff[[i]]) #Generating the DSA result per parameter.
}
save(dsa.results,file="dsa_eff_out.rdata") #save the result

dsa.results2 <- list()
for (i in 1:2) {
 dsa.results2 [[i]] <- dsa.model.run(dsa_pPFS2PD.UC[[i]]) #dsa for transition probability to PD state.
}
save(dsa.results,file="dsa_pPFS2PD.UC_out.rdata") #save the result.

dsa.results3 <- list()
for (i in 1:2) {
 dsa.results3 [[i]] <- dsa.model.run(dsa_pPD2D[[i]]) #dsa for transition probability from PD to dead.
}
save(dsa.results,file="dsa_pPD2D_out.rdata")

dsa.results4 <- list()
for (i in 1:2) {
 dsa.results4 [[i]] <- dsa.model.run(dsa_pPFS2D[[i]]) #dsa for transition probability from PFS to dead.
}

dsa.results5 <- list()
for (i in 1:2) {
 dsa.results5 [[i]] <- dsa.model.run(dsa_pBiomarker[[i]]) #dsa for biomarker prevalence/frequency.
}

dsa.results6 <- list()
for (i in 1:2) {
 dsa.results6 [[i]] <- dsa.model.run(dsa_pSensitivity[[i]]) #dsa for testing sensitivity.
}

dsa.results7 <- list()
for (i in 1:2) {
 dsa.results7 [[i]] <- dsa.model.run(dsa_pSpecificity[[i]]) #dsa for testing specificity.
}

```

```

dsa.results8 <- list()
for (i in 1:2) {
 dsa.results8 [[i]] <- dsa.model.run(dsa_cPFS[[i]]) #dsa for health state costs in PFS.
}

dsa.results9 <- list()
for (i in 1:2) {
 dsa.results9 [[i]] <- dsa.model.run(dsa_cPD[[i]]) #dsa for health state costs in PD.
}

dsa.results10 <- list()
for (i in 1:2) {
 dsa.results10 [[i]] <- dsa.model.run(dsa_cTest[[i]]) #dsa for testing cost.
}

dsa.results11 <- list()
for (i in 1:2) {
 dsa.results11 [[i]] <- dsa.model.run(dsa_uPFS.UC[[i]]) #dsa for utility value in PFS (treated with UC).
}

dsa.results12 <- list()
for (i in 1:2) {
 dsa.results12 [[i]] <- dsa.model.run(dsa_uPFS.TC[[i]]) #dsa for utility value in PFS (treated with TC).
}

dsa.results13 <- list()
for (i in 1:2) {
 dsa.results13 [[i]] <- dsa.model.run(dsa_uPD.UC[[i]]) #dsa for utility value in PD (treated with UC).
}

dsa.results14 <- list()
for (i in 1:2) {
 dsa.results14 [[i]] <- dsa.model.run(dsa_uPD.TC[[i]]) #dsa for utility value in PD (treated with TC).
}

dsa.results <- data.frame(dsa.results1,dsa.results2) #Create the dataframe of all DSA results.
for (i in 1:14) {
}

#5. Calculate the incremental costs and QALYs
#convert the dataset in the form of 'list' to the form of 'data.frame'
dsa.results_dataframe <- data.frame(Reduce(rbind,dsa.results))
incCosts_TT_UC <- dsa.results_dataframe[, "costTT"] - dsa.results_dataframe[, "costUC"]
incCosts_TT_TC <- dsa.results_dataframe[, "costTT"] - dsa.results_dataframe[, "costTC"]
incQalys_TT_UC <- dsa.results_dataframe[, "qalyTT"] - dsa.results_dataframe[, "qalyUC"]
incQalys_TT_TC <- dsa.results_dataframe[, "qalyTT"] - dsa.results_dataframe[, "qalyTC"]
incCosts_TC_UC <- dsa.results_dataframe[, "costTC"] - dsa.results_dataframe[, "costUC"]
incQalys_TC_UC <- dsa.results_dataframe[, "qalyTC"] - dsa.results_dataframe[, "qalyUC"]

summary(incCosts_TT_UC)
summary(incCosts_TT_TC)

```

```
summary(incCosts_TC_UC)
summary(incQalys_TT_TC)
summary(incQalys_TT_UC)
summary(incQalys_TC_UC)
```

*#6. Calculate ICER*

```
dsaICER_TT_UC = mean(incCosts_TT_UC)/mean(incQalys_TT_UC)
dsaICER_TT_TC = mean(incCosts_TT_TC)/mean(incQalys_TT_TC)
dsaICER_TC_UC = mean(incCosts_TC_UC)/mean(incQalys_TC_UC)
```